

# PATHOLOGY

**Q. The study of pathology includes (BSMMU –Residency - MD/MS, Basic science – March '14)**

- a) knowledge about etiology
- b) skill of preparation of histopathology slides
- c) understanding pathogenesis of diseases
- d) recognizing changes in tissues
- e) only diagnosis of histopathology and cytology slides

Ans. a) T b) T c) T d) T e) F

**Help link:**

Pathology is the study (*logos*) of disease (*pathos*). More specifically, it is devoted to the study of the structural, biochemical, and functional changes in cells, tissues, and organs that underlie disease. By the use of molecular, microbiologic, immunologic, and morphologic techniques, pathology attempts to explain the whys and wherefores of the signs and symptoms manifested by patients while providing a rational basis for clinical care and therapy. It thus serves as the bridge between the basic sciences and clinical medicine, and is the scientific foundation for all of medicine.

**Core of pathology:**

The four aspects of a disease process that form the core of pathology are

1. its cause (*etiology*),
2. the mechanisms of its development (*pathogenesis*),
3. the biochemical and structural alterations induced in the cells and organs of the body (*molecular and morphologic changes*), and
4. the functional consequences of these changes (*clinical manifestations*).

(Ref: Robbins & Cotrans-9<sup>th</sup>, P-31-32)

**Q. The following statements are correctly paired - (BSMMU-MS-01Ja)**

- |  |   |
|--|---|
| a) Idiopathic – cause known                    | F |
| b) Pathogenesis – direct cause of disease      | F |
| c) Congenital – present at birth               | T |
| d) Prognosis – likely disease outcome          | T |
| e) Aetiology – Mechanism of disease production | F |

## The cell as a unit of health and disease

**The Genome**

The sequencing of the human genome represented a landmark achievement of biomedical science. Published in draft form in 2001 and more completely detailed in 2003, the information has already led to remarkable advances in science and medicine. Since then there has been an exponential decrease in the cost of sequencing and an exponential increase in data accrual; this new information, now literally at our fingertips, promises to revolutionize our understanding of health and disease. However, the sheer volume of the data is formidable, and there is a dawning realization that we have only begun to scratch the surface of its complexity; uncovering the relevance to

disease and then developing new therapies remain challenges that both excite and inspire scientists and the lay public alike.

(Ref: Robbins & Cotrans-9<sup>th</sup>, P-1)

**Noncoding DNA**

The human genome contains roughly 3.2 billion DNA base pairs. Within the genome there are about 20,000

protein-encoding genes, comprising only about 1.5% of the genome. These proteins variously function as enzymes, structural components, and signaling molecules and are used to assemble and maintain all of the cells in the body.

80% of the human genome either binds proteins, implying it is involved in regulating gene expression, or can be assigned some functional activity, mostly related to the regulation of gene expression, often in a cell-type specific fashion.

The major classes of functional non-protein-coding sequences found in the human genome are the following:

- Promoter and enhancer regions that provide binding sites for transcription factors
- Binding sites for factors that organize and maintain higher order chromatin structures
- Noncoding regulatory RNAs. More than 60% of the genome is transcribed into RNAs that are never translated into protein, but which nevertheless can regulate gene expression through a variety of mechanisms. The two best-studied varieties—micro-RNAs and long non-coding RNAs—are described later.
- Mobile genetic elements (e.g., transposons). Remarkably, more than one third of the human genome is composed of these elements, popularly denoted as “jumping genes.” These segments can move around the genome, exhibiting wide variation in number and positioning even amongst closely related species (i.e., humans and other primates). They are implicated in gene regulation and chromatin organization, but their function is still not well established.
- Special structural regions of DNA, in particular telomeres (chromosome ends) and centromeres (chromosome “tethers”)

### Cell cycle

The cell cycle is reckoned to begin at the completion of one cell division (mitosis) and to end at the completion of the next division. The time taken for one cell cycle is the generation time.

■ **Phases of interphase:** The interphase is subdivided into following phases:

1. G<sub>1</sub> (pre-synthesis) phase
2. S (DNA synthesis) phase
3. G<sub>2</sub> (pre-mitotic) phase.
4. M (mitotic) phase

(Ref: Robbins & Cotran-9<sup>th</sup>, P-25)

Cells that become highly differentiated after the last mitotic event may cease to undergo mitosis permanently (e.g. neurons, muscle cells). These cells do not enter the cell cycle and are said to be in a resting stage, the **G<sub>0</sub> (outside) phase**.

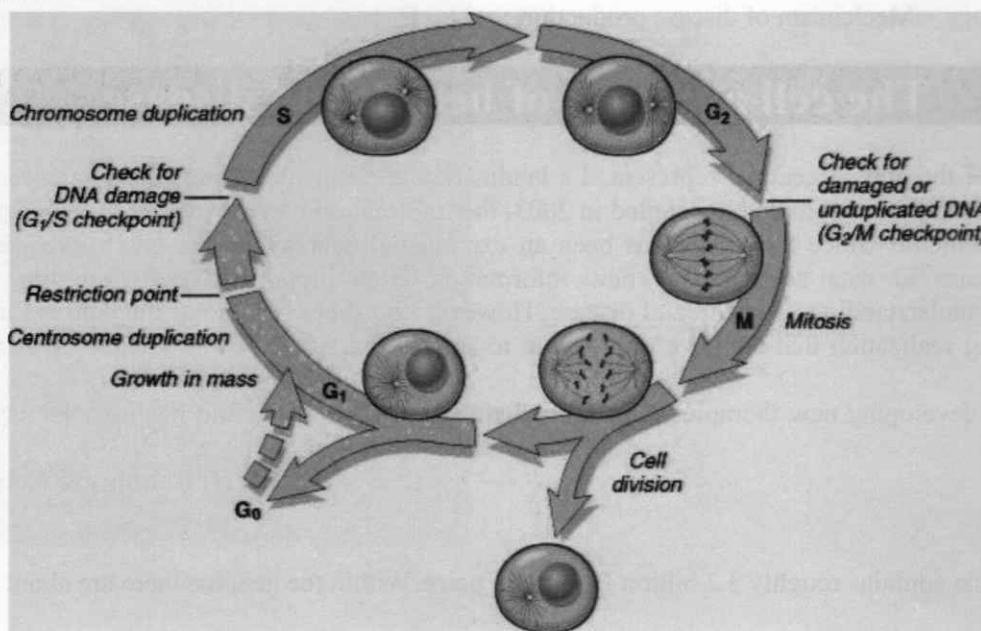


Fig: Cell cycle.

Phases	Features
<b>G1 Phase</b>	1. The daughter cells formed during mitosis enter the G1 phase. 2. During this phase the cells synthesize RNA, regulatory proteins essential to DNA replication, and enzymes for these synthetic activities.
<b>S Phase</b>	1. It is the synthetic phase of the cell cycle when the genome is duplicated. 2. The cell now contains twice the normal complement of its DNA, that is -the (2n) amount of DNA is doubled (4n) in preparation for cell division.
<b>G2 Phase</b>	1. RNA and proteins essential to cell division are synthesized. 2. The energy for mitosis is also stored.
<b>M phase</b>	The short period of time when the cell divides its nucleus and cytoplasm, giving rise to two daughter cells. This occurs through 4 phases: prophase, metaphase, anaphase, and telophase.

### Stem cell

#### Definition:

Stem cells are undifferentiated biological cells that can differentiate into specialized cells and can divide (through mitosis) to produce more stem cells

#### Stem cells are characterized by two important properties:

- Self-renewal, which permits stem cells to maintain their numbers.
- Asymmetric division, in which one daughter cell enters a differentiation pathway and gives rise to mature cells, while the other remains undifferentiated and retains its self-renewal capacity.

#### Embryonic Stem cells:

Are pluripotent cells that can generate all tissue of the body. It can give rise to multipotent stem cells and cause lineage committed stem cells and differentiated into 3 embryonic layers.

#### Adult (Somatic stem cells) :

Restricted capacity to generate different cell types.

#### Niches:

Somatic stem cells reside in special microenvironment composed of- Mesenchymal, endothelial and other cell types.

Growth factors	Sources	Functions
<b>Epidermal growth factor (EGF)</b>	Activated macrophages, salivary glands, keratinocytes, and many other cells	<ul style="list-style-type: none"> <li>Mitogenic for keratinocytes and fibroblasts</li> <li>Stimulates keratinocyte migration</li> <li>Stimulates formation of granulation tissue.</li> </ul>
<b>Transforming growth factor <math>\alpha</math> (TGF-<math>\alpha</math>)</b>	Activated macrophages, keratinocytes, and many other cell types	Stimulates proliferation of hepatocytes and many other epithelial cells
<b>Hepatocyte growth factor (HGF) (scatter factor)</b>	Fibroblasts, stromal cells in the liver, endothelial cells	Enhances proliferation of hepatocytes and other epithelial cells; increases cell motility
<b>Vascular endothelial growth factor (VEGF)</b>	Mesenchymal cells	Stimulates proliferation of endothelial cells; increases vascular permeability
<b>Platelet-derived growth factor (PDGF)</b>	Platelets, macrophages, endothelial cells, smooth muscle cells, keratinocytes	Chemotactic for neutrophils, macrophages, fibroblasts, and smooth muscle cells; activates and stimulates proliferation of fibroblasts, endothelial, and other cells; stimulates ECM protein synthesis
<b>Fibroblast growth factors (FGFs), including acidic (FGF-1) and basic (FGF-2)</b>	Macrophages, mast cells, endothelial cells, many other cell types	Chemotactic and mitogenic for fibroblasts; stimulates angiogenesis and ECM protein synthesis
<b>Transforming growth factor-<math>\beta</math> (TGF-<math>\beta</math>)</b>	Platelets, T lymphocytes, macrophages, endothelial cells, keratinocytes, smooth muscle cells, fibroblasts	Chemotactic for leukocytes and fibroblasts; stimulates ECM protein synthesis; suppresses acute inflammation
<b>Keratinocyte growth factor (KGF) (i.e., FGF-7)</b>	Fibroblasts	Stimulates keratinocyte migration, proliferation, and differentiation

(Ref: Robbins & Cotran-9<sup>th</sup>, P-19)

# Cellular Adaptation, Cell Injury & Cell death

## Cellular Adaptation

■ **Cellular adaptation:** *Adaptations* are reversible functional and structural responses to changes in physiologic stresses (e.g. pregnancy) and some pathologic stimuli, during which new but altered steady states are achieved, allowing the cell to survive and continue to function.

Adaptations are reversible changes in the size, number, phenotype, metabolic activity, or functions of cells in response to changes in their environment.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-32-34)

The adaptive changes are:

1. Hyperplasia
2. Hypertrophy
3. Atrophy
4. Metaplasia

Cellular & tissue responses to injury depends on:

(Ref: Robbins & Cotran-9<sup>th</sup>, P-33)

**Cellular and tissue responses to different types of injury:** Cellular response to injury varies in its effects on cell structure and function according to the type of cell involved and the nature and severity of the agent responsible. They include-

### 1. Cellular adaptations:

- Hyperplasia, hypertrophy
- Atrophy
- Metaplasia

### 2. Cell injury

- Acute reversible cell injury  
Cellular swelling fatty change
- Irreversible injury → cell death  
Necrosis  
Apoptosis

### 3. Intracellular accumulations

### 4. Pathological calcifications

### 5. Cellular aging

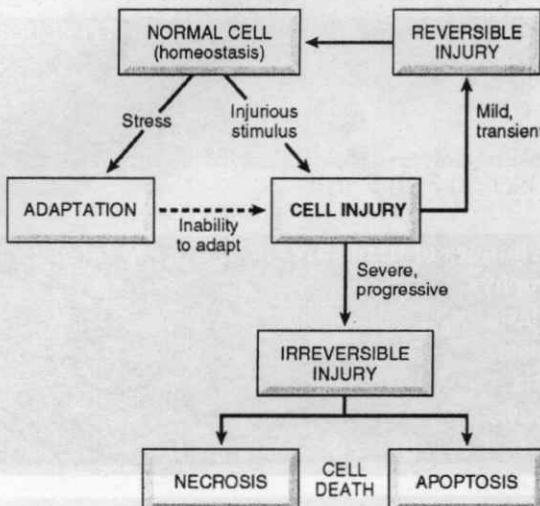


Fig: Stages of the cellular response to stress and injurious stimuli

(Ref: Robbins & Cotran-9<sup>th</sup>, P-32)

### Cellular Adaptations to Stress

- **Hypertrophy:** increased cell and organ size, often in response to increased workload; induced by growth factors produced in response to mechanical stress or other stimuli; occurs in tissues incapable of cell division
- **Hyperplasia:** increased cell numbers in response to hormones and other growth factors; occurs in tissues whose cells are able to divide or contain abundant tissue stem cells.
- **Atrophy:** decreased cell and organ size, as a result of decreased nutrient supply or disuse; associated with decreased synthesis of cellular building blocks and increased breakdown of cellular organelles
- **Metaplasia:** change in phenotype of differentiated cells often in response to chronic irritation, that makes cells better able to withstand the stress; usually induced by altered differentiation pathway of tissue stem cells; may result in reduced functions or increased propensity for malignant transformation.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-38)

Question Bank

**Q. Cellular responses to injury are (BSMMU – Non-Residency – MD, MS, Paediatrics, Basic Science, Dentistry – July' 19)**

- a) necrosis
- b) fatty change
- c) calcification
- d) hyperplasia
- e) neoplasia

Ans. a) T b) T c) T d) T e) F

(Ref. Robbins-9<sup>th</sup>, P-33)

**Q. Cellular responses to nonlethal stimuli are (BSMMU – Residency - Dentistry – March' 19)**

- a) calcification
- b) metaplasia
- c) hypertrophy
- d) fibrosis
- e) fatty change

Ans. a) F b) T c) T d) F e) F

(Ref. Robbins-9<sup>th</sup>, P-33)

**Help Link:**

Adaptive disorders are the adjustments which the cells make in response to stresses which may be for physiologic needs (physiologic adaptation) or a response to non-lethal pathologic injury (pathologic adaptation).

(Ref. Harsh Mohan-7<sup>th</sup>, P-37)

**Q. Cellular adaptations to stress are (BSMMU – Residency – Dentistry – March' 18)**

- a) hypertrophy
- b) hyperplasia
- c) neoplasia
- d) dysplasia
- e) metaplasia

Ans. a) T b) T c) F d) F e) T

**Q. Adaptive changes of tissue are (BSMMU – Residency - MD, MS, Basic Science, Dentistry - March' 17)**

- a) hypertrophy
- b) hyperplasia
- c) metaplasia
- d) dysplasia
- e) dystrophy

Ans. a) T b) T c) T d) F e) F

**Q. The cellular adaptation includes (BSMMU – Non-Residency – MD, MS, Basic science, Dentistry – July' 16)**

- |                  |   |
|------------------|---|
| a) hyperplasia   | T |
| b) atrophy       | T |
| c) apoptosis     | F |
| d) calcification | F |
| e) hypertrophy   | T |

**Q. Adaptive changes of tissue are (BSMMU – Residency – MD, MS, Basic science, Dentistry – March' 16)**

- |                |   |
|----------------|---|
| a) hypertrophy | T |
| b) hyperplasia | T |
| c) dysplasia   | F |
| d) metaplasia  | T |
| e) metastasis  | F |

(Ref. Robbins-9<sup>th</sup>, P-38)

**Q. Cellular adaptations are:** (BSMMU - M. Phil, Diploma - July '10)

- |                |   |
|----------------|---|
| a) Agenesis    | F |
| b) Atrophy     | T |
| c) Metaplasia  | T |
| d) Dysplasia   | F |
| e) Hyperplasia | T |

**Q. The cellular response to injurious stimuli depends -** (MD/MS (DMC)-09Ja)

- |                                |   |
|--------------------------------|---|
| a. on type of injury           | T |
| b. duration of stimulus        | T |
| c. severity of injurious agent | T |
| d. temperature of environment  | F |
| e. nutritional state           | T |

**HELP LINK:**

**Cellular and tissue Responses & consequences to Injury** depends on:

- Type of cell involved
  - Nature & severity of the agent responsible
  - Duration of injury
  - Nutritional status
  - Vascularity of the tissue
- (Ref: Robbin's -9<sup>th</sup>, P-44, 45; Prof. Khaleque, P-1)

**Q. Following are the cellular adaptive changes:** (MD/MS (DMC)-08Ja)

- |                |   |
|----------------|---|
| a) hyperplasia | T |
| b) neoplasia   | F |
| c) hypertrophy | T |
| d) dysplasia   | F |
| e) atrophy     | T |

**Q. In response to injury, the following are the examples of cellular adaptations.** (MD/MS (DMC)-05Ja)

- |                             |   |
|-----------------------------|---|
| a) Atrophy                  | T |
| b) Apoptosis                | F |
| c) Hypertrophy              | T |
| d) Metaplasia               | T |
| e) Metastatic calcification | F |

## HYPERTROPHY

**Q. Hypertrophy is associated with an** (BSMMU - Residency - MD/MS, Basic science, Paediatrics, Dentistry - March '19)

- a) increase in the number of mitosis
- b) increase in the bulk of a tissue or organ
- c) increase in the number of cells in an organ or tissue
- d) absolute decrease in interstitial tissue
- e) increase in functional capacity of organs

Ans. a) F b) T c) F d) F e) T

(Ref: Robbins-9<sup>th</sup>, P-34 + Harsh Mohan textbook of Pathology-7<sup>th</sup>, P-39)

**HELP LINK:**

progesterone  
binding with estrogen receptor

■ **Hypertrophy:** Hypertrophy refers to an increase in the size of cells, resulting in an increase in the size of the organ. The hypertrophied organ has no new cells, just larger cells. The increased size of the cells is due to the synthesis of more structural components of the cells.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-34)

Or,  
Hypertrophy refers to an increase in the size of an organ due to an increase in the size of its constitutional cells.

■ **Causes:**

1. Increased functional demand.
2. Stimulation by hormones and growth factors.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-34)

■ **Types:**

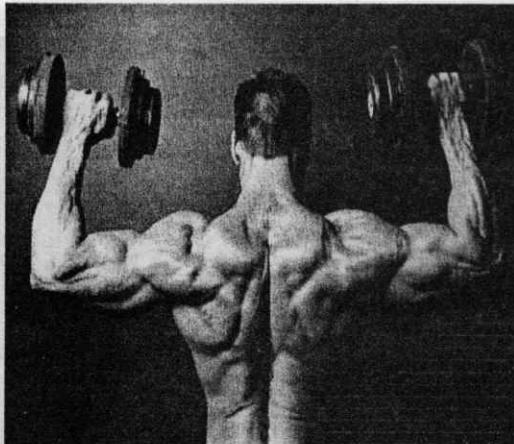
1. **Physiological:**

- Pregnant uterus.
- Hypertrophy of breast during lactation due to prolactin & estrogen.
- The skeletal muscles due to heavy work as an adaptive response. eg. Body builders.

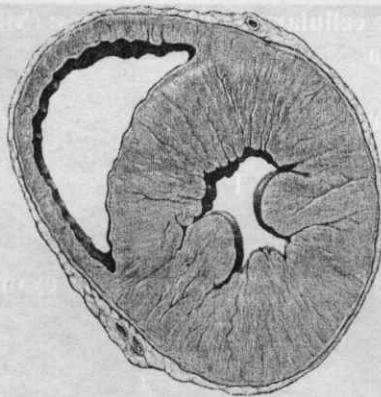
2. **Pathological:**

- Left ventricular hypertrophy- hypertrophy of myocytes in left ventricle in systemic hypertension, aortic stenosis, mitral regurgitation due to increased workload.
- Hypertrophy of a kidney is seen if the other kidney is damaged, removed or congenitally absent.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-34)



**Fig: Physiological hypertrophy**



**Fig: Pathological hypertrophy**

**Question Bank**

**Q. Hypertrophy refers to (BSMMU –Residency – MD, MS, Basic Science, Dentistry – March '18)**

- a) increase in the size of cells
- b) increase in the number of cells
- c) increase in the size of affected organs
- d) increased production of cellular proteins
- e) increased accumulation of cellular lipids

Ans. a) T b) F c) T d) T e) F

**Q. Hypertrophy of an organ (BSMMU –Residency - MD/MS, Basic science – March' 14)**

- a) means increased size due to increased number of cells
- b) is always a pathological process
- c) is not seen where permanent cells make up the tissue
- d) is prone to ischaemia
- e) is a reversible process

Ans. a) F b) F c) F d) T e) T

**Q. Hypertrophy- (MD/MS (DMC)-04Ja)**

- a) Means increase in cell number F
- b) Is always found in pathological condition F
- c) occurs in labile cells only. F
- d) is never found in myocardium F
- e) results from cell swelling. F

(due to increased structural component)

## HYPERPLASIA

■ **Hyperplasia:** Hyperplasia is defined as an increase in the number of cells in an organ or tissue in response to stimulus. Although hyperplasia and hypertrophy are distinct processes, they frequently occur together, and may be triggered by the same external stimulus.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-35)

■ **Types:**

1. **Physiological:**

◆ **Hormonal hyperplasia:** which increases the functional capacity of a tissue when needed.

• Female breast - during puberty, pregnancy & lactation.

• Uterus: during pregnancy

• Bone marrow hyperplasia in hemolytic anaemia (Ref: Robbins & Cotran-9<sup>th</sup>, P-36)

◆ **Compensatory hyperplasia:** which increases tissue mass after damage or partial resection.

• Hyperplasia that occurs after partial hepatectomy.

• After unilateral nephrectomy, when the remaining kidney undergoes compensatory hyperplasia

2. **Pathological:**

• Hyperplasia of endometrium in granulosa tumor of ovary.

• Hyperplasia in wound healing- proliferation of blood vessels & fibroblast.

• Hyperplasia & hypertrophy in thyroid gland- colloid goiter, Grave's disease.

• Nodular hyperplasia of prostate (by androgen)

• Skin warts due to papillomavirus.

**Mechanism of Hyperplasia:**

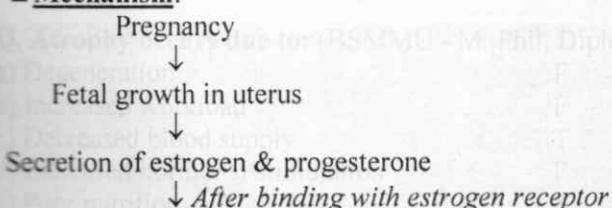
Hyperplasia is the result of growth factor-driven proliferation of mature cells and, in some cases, by increased output of new cells from tissue stem cells. For instance, after partial hepatectomy growth factors are produced in the liver that engage receptors on the surviving cells and activate signaling pathways that stimulate cell proliferation. But if the proliferative capacity of the liver cells is compromised, as in some forms of hepatitis causing cell injury, hepatocytes can instead regenerate from intrahepatic stem cells.

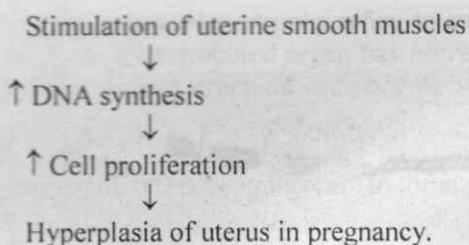
(Ref: Robbins & Cotran-9<sup>th</sup>, P-36)

**Discussion of hyperplasia of uterus in pregnancy:**

Hyperplasia of uterus means an increase in the number of cells in endometrium, which also have increased volume. It occurs in pregnancy due to hormonal effect.

■ **Mechanism:**





#### Risk of hyperplasia:

##### Cancer formation in the following types

- Endometrial hyperplasia
- Atypical ductal hyperplasia of breast (fibrocystic change)

#### Question Bank

**Q. Cells that undergo hyperplasia on stimulation are (BSMMU – Residency - MD/MS, Basic science, Paediatrics – March '19)**

- a) hepatocytes
- b) cardiac myocytes
- c) uterine smooth muscle cells
- d) neurons
- e) thyroid follicular cells

Ans. a) T b) F c) T

d) F (Neurons, cardiac and skeletal muscle) have little or no capacity for regenerative hyperplastic growth.

e) T

**Help link: Hyperplasia occurs due to increased recruitment of cells from G0 (resting) phase of the cell cycle to undergo mitosis, when stimulated.**

- ✓ All body cells do not possess hyperplastic growth potential.
- ✓ Labile cells (e.g. epithelial cells of the skin and mucous membranes, cells of the bone marrow and lymph nodes) and Stable cells (e.g. parenchymal cells of the liver, pancreas, kidney, adrenal, and thyroid) can undergo hyperplasia,
- ✓ Permanent cells (e.g. neurons, cardiac and skeletal muscle) have little or no capacity for regenerative hyperplastic growth.

(Ref: Harsh Mohan textbook of Pathology-7<sup>th</sup>, P-39)

**Q. Precursors for malignancy are - (BSMMU – Non-Residency – MD, MS, Basic Science & Dentistry – July '17)**

- a) hypertrophy
- b) hyperplasia
- c) metaplasia
- d) atrophy
- e) dysplasia

Ans. a) F b) T c) T d) F e) T

**Q. Hyperplasia (BSMMU – Non-Residency – MD, MS, Basic science, Dentistry – July '15)**

- a) results in increased cell size F
- b) results in increased cell numbers T
- c) occurs in myocardium F
- d) occurs in uterus due to increased number of cells T
- e) occurs in brain tissue F

Ans. a) is a reversible process  
b) is prone to neoplasia  
c) is a reversible process

**Q. The following hyperplastic conditions are associated with increased risk of malignancy (BSMMU – Residency - MD/MS, Basic science – March' 14)**

- |   |   |
|---|---|
| a) nodular hyperplasia of prostate        | F |
| b) nodular goitre                         | F |
| c) endometrial hyperplasia                | T |
| d) ductal hyperplasia of breasts          | T |
| e) hyperplasia of uterine smooth muscles. | F |

**Q. Hyperplasia (BSMMU – Non-Residency - MD/MS, Basic science – 13Ju)**

- a) is seen in organs made of labile cells
- b) is a reversible adaptive change
- c) is never associated with hypertrophy
- d) is seen in epithelium only
- e) may lead to malignancy in some cases

Ans. a) T b) T c) F d) F (connective tissue also) e) T

**Q. Pathologic hyperplasia associated with an increased risk of malignancy includes: (BSMMU – MD – January, 2010)**

- |  |   |
|--|---|
| a) endometrial hyperplasia                     | T |
| b) nodular prostatic hyperplasia               | F |
| c) atypical ductal hyperplasia of breast       | T |
| d) hyperplasia of gastric pits                 | F |
| e) chief cell hyperplasia of parathyroid gland | F |

**Q. Following types of hyperplasia may lead to cancer formation: (BSMMU - M. Phil, Diploma, July-09)**

- a) Endometrial hyperplasia T
- b) Hyperplasia of uterine smooth muscle in pregnancy F
- c) Nodular hyperplasia of prostate F
- d) Compensatory hyperplasia in remaining kidney after unilateral nephrectomy F
- e) Stem cell hyperplasia after some type of cell loss. F

**Q. Hyperplasia occurs in following clinical settings: (BSMMU - M. Phil, Diploma, July-07)**

- a) Heart after myocardial infarction F
- b) Bone marrow in hemolytic anaemia T
- c) Epidermis in viral wart T
- d) Seminiferous tubules in undescended testis F
- e) Lymphnode in antigenic stimulation T

**Q. Hyperplasia (M. phil, Diploma (DMC) – 03Ju)**

- a) Constitutes an increase in cell number in an organ T
- b) Is always pathological F
- c) Is an adaptive change T
- d) Occurs in permanent cells F
- e) Constitutes a fertile soil for cancerous proliferation T

## ATROPHY

**Q. Atrophy occurs due to: (BSMMU - M. Phil, Diploma, July-09)**

- a) Degeneration F
- b) Increased workload F
- c) Decreased blood supply T
- d) Increased hormonal stimulation F
- e) Poor nutrition T

**HELP LINK:**

■ **Definition:** Atrophy is defined as a reduction in size of an organ or tissue due to decrease in cell size and number.

■ **Types:**1. **Physiological:**

- i. Atrophy during fetal development- Atrophy of notocord or thyroglossal duct.
- ii. Uterus decreases in size after parturition.

2. **Pathological:**

- i. Local: Ischemic atrophy, Disuse atrophy, Pressure atrophy, Hormonal atrophy.
- ii. Generalized atrophy: Due to starvation, Senile atrophy due to aging.

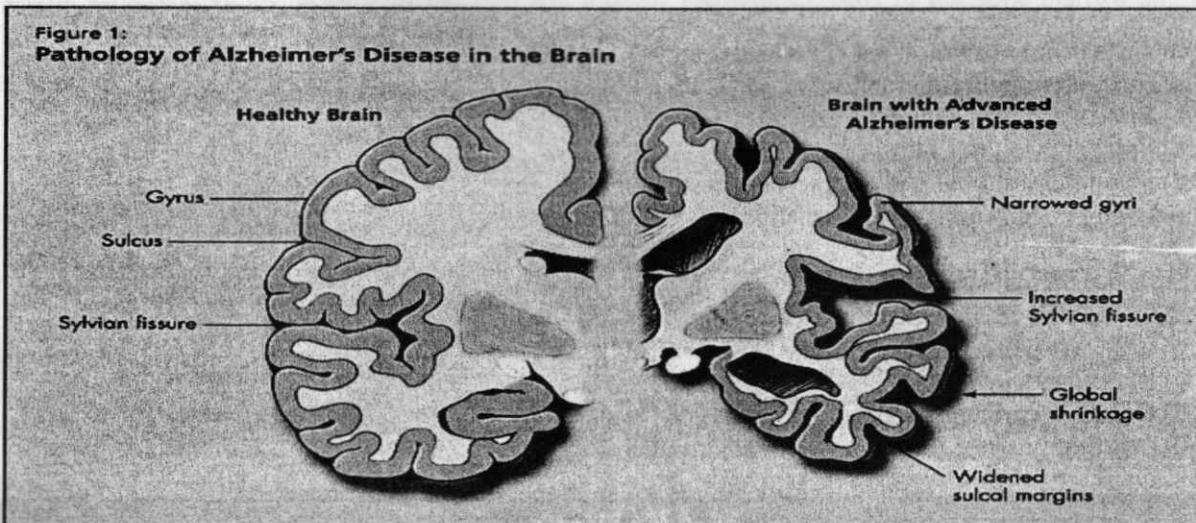
■ **Common causes of atrophy:**

1. **Decreased workload (atrophy of disuse)** eg. Skeletal muscle atrophy in a patient restricted to complete bed rest or when a broken limb is immobilized in a plaster cast.
2. **Loss of innervation (denervation atrophy)**, eg. Atrophy of the muscle fibres due to damage of the supplying nerves.
3. **Diminished blood supply**, eg. Brain undergoes progressive atrophy due to atherosclerosis in cerebral vessels.
4. **Inadequate nutrition**, eg. Marked muscle wasting (cachexia) in profound protein-calorie malnutrition (marasmus), chronic inflammatory diseases and cancer.
5. **Loss of endocrine stimulation**, eg. loss of estrogen stimulation after menopause results in physiologic atrophy of the endometrium, vaginal epithelium & breast.
6. **Aging (senile atrophy)** is seen in the brain & heart.
7. **Pressure**: Atrophy occurs due to tissue compression for a long time, eg. An enlarging benign tumor can cause atrophy in the surrounding compressed tissues.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-36, 37)

**Mechanism of atrophy:**

- Decreased protein synthesis and increased protein degradation by ubiquitin-proteasome pathway.
- Autophagy (self eating): Brown atrophy of heart

**Q. Pathological atrophy of an organ:** (BSMMU – MD/MS - January, 2008)

- |                                       |   |
|---------------------------------------|---|
| a) is seen in old age                 | T |
| b) is caused by coagulation necrosis  | F |
| c) causes shrinkage in size           | T |
| d) can be recognized under microscope | T |
| e) is primarily due to genetic defect | F |

## METAPLASIA

■ **Definition:** Metaplasia is a reversible change in which one differentiated cell type (epithelial or mesenchymal) is replaced by another cell type.

It does not result from a change in the phenotype of a differentiated cell types.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-37)

■ **Types:** 2 types.

1. **Epithelial metaplasia:**

i. **Squamous metaplasia:** The most common epithelial metaplasia is columnar to squamous

- In the habitual smoker, the normal ciliated columnar epithelial cells of the trachea & bronchi are often replaced by stratified squamous epithelial cells. This occurs in the respiratory tract in response to chronic irritation.

- Stones in the excretory ducts of the salivary glands, pancreas, or bile ducts may cause replacement of the normal secretory columnar epithelium by stratified squamous epithelium.

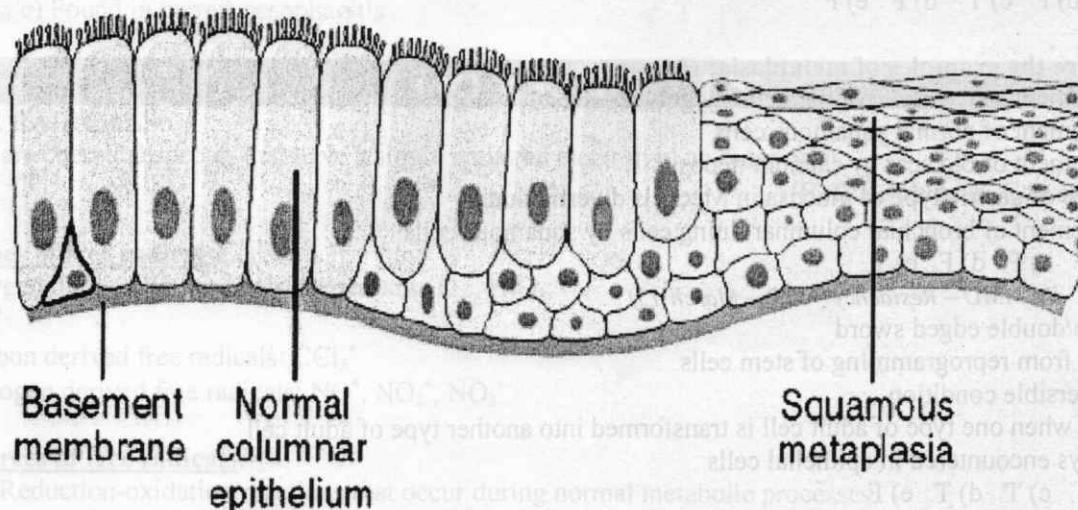
- A deficiency of vitamin A (retinoic acid) induces squamous metaplasia in the respiratory epithelium.

ii. **Columnar metaplasia:**

- In Barrett esophagitis, the squamous esophageal epithelium is replaced by intestinal like columnar cells under the influence of refluxed gastric acid. Cancers may arise in these areas; these are typically glandular (adeno) carcinomas.

2. **Connective tissue metaplasia:** Connective tissue metaplasia is the formation of cartilage, bone, or adipose tissue (mesenchymal tissues) in tissues that normally do not contain these elements. For example, bone formation in muscle, designated **myositis ossificans**, occasionally occurs after intramuscular haemorrhage.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-38)



### Regarding metaplasia:

- Is called double edged sword
- Is a fertile soil for cancer development.
- Mechanisms:
  - Reprogramming of stem cells in the undifferentiated mesenchymal cells in the connective tissue.
  - Chronic irritation, Expression of genes, external stimuli, transcription factors are also associated.



**Question Bank**

**Q. Metaplasia (BSMMU – Residency - Dentistry – March' 19)**

- a) occurs due to reprogramming of stem cells
- b) results from persistent irritation
- c) may result from ingestion of certain drugs
- d) always occurs in epithelial cells
- e) may progress to dysplasia

Ans: a) T b) T c) F d) F (also in mesenchymal tissue) e) T

(Ref. Robbins-9<sup>th</sup>, P-38)

**Q. Metaplasia is (BSMMU – Residency - Dentistry - March' 17)**

- a) an adaptive change
- b) irreversible
- c) characterized by increased size of cells
- d) linked to cancer development
- e) preceded by hyperplasia

Ans. a) T b) F c) F d) T e) F

**Q. Barret's oesophagus (BSMMU – Residency – MD, MS, Basic Science – March' 15)**

- a) is associated with prolonged reflux oesophagitis
- b) is characterized by change of glandular epithelium to squamous epithelium
- c) may lead to adenocarcinoma
- d) is an example of hyperplasia
- e) is a neoplastic condition

Ans. a) T b) F c) T d) F e) F

**Q. Following are the examples of metaplasia: (BSMMU – Residency – MD/MS – March'13)**

- a) Replacement of gastric foveolar cells by goblet cells
- b) Replacement of normal squamous cells
- c) Replacement of old scar by calcium deposits
- d) Presence of gastric type of mucosa in Meckels diverticulum
- e) Replacement of bronchial columnar lining cells by squamous cells

Ans : a) T b) F c) F d) F e) T

**Q. Metaplasia: (BSMMU – Residency – MD – March'13)**

- a) Is a two/double edged sword
- b) Results from reprogramming of stem cells
- c) Is a reversible condition
- d) Results when one type of adult cell is transformed into another type of adult cell
- e) Is always encountered in epithelial cells

Ans : a) T b) T c) T d) T e) F

**Q. Metaplasia: (BSMMU- M. Phil, Diploma (Non-Residency)-March-2012, DMC & others-MD/MS-March-12)**

- |  |   |
|--|---|
| a) is an irreversible change                 | F |
| b) is an adaptive change                     | T |
| c) occurs only in epithelial tissues         | F |
| d) is linked to cancer development           | T |
| e) occurs in bronchial epithelium in smokers | T |

**Q. Metaplasia (BSMMU – MD/MS (Residency) – January, 2011)**

- |  |   |
|--|---|
| a) is an irreversible change   | F |
| b) results from reprogramming of stem cells that exist in normal tissues | T |
| c) is an adaptive response   | T |
| d) occurs only in epithelial cells / tissues                             | F |
| e) means disordered growth   | F |

**Q. Metaplasia:** (BSMMU - M. Phil, Diploma, July-08)

- a) results from a change in the phenotype of a differentiated cell type F [Robbins-9<sup>th</sup>, P-38]
- b) results from reprogramming of stem cells that exist in normal tissues T
- c) is a reversible change T
- d) may turn into malignancy if the stimulus persists T
- e) occurs only in epithelial tissues F

**Q. Metaplasia is characterized by:** (MD/MS (DMC)-04Ja)

- a) an increase in the number and size of the cell F
- b) variation in the size & shape of the cells F
- c) an increase in the nucleo-cytoplasmic ratio of cells. F
- d) cloudy swelling of the cells F
- e) an acute inflammatory reaction. F

**Q. Regarding metaplasia-** (BIRDEM-04)

- a) It often precedes malignancy T
- b) Usual site is cervix of multipara F
- c) Majority cells are columnar to squamous T
- d) Chronic irritation is important in its genesis T
- e) It is an irreversible state F

**Q. Metaplasia is-** (MD/MS (DMC)-03Ja)

- a) An irreversible change F
- b) Commonly occurs in gastrointestinal tract F
- c) Caused by vit- A deficiency T
- d) An undesirable change in most circumstances T
- e) Found in barrett oesophagitis T

**FREE RADICALS****FREE RADICALS:**

These are chemical species that have a single unpaired electron in an outer orbit.

(Ref: Robbins & Cotrans – 9<sup>th</sup>, P-47)

**■ Types of free radicals:**

1. Oxygen derived free radicals: Superoxide  $O_2^-$ ,  $H_2O_2$ ,  $OH^\bullet$
2. Carbon derived free radicals:  $CCl_3^\bullet$
3. Nitrogen derived free radicals:  $NO^\bullet$ ,  $NO_2^\bullet$ ,  $NO_3^-$

**■ Sources of free radicals:**

1. Reduction-oxidation reactions that occur during normal metabolic processes.
2. Absorption of radiant energy (e.g. UV light, X-ray)
3. Activated leukocytes during inflammation.
4. Enzymatic metabolism of exogenous chemicals or drugs ( $CCl_4$  to  $CCl_3^\bullet$ )
5. Transition metals (eg. Fe & Cu)
6. Nitric oxide (NO).

**Generation of free radicals:**

Free radicals may be generated within cells in several ways:

1. **The reduction-oxidation reactions that occur during normal metabolic processes.** During normal respiration, molecular  $O_2$  is reduced by the transfer of four electrons to  $H_2$  to generate two water molecules. This conversion is catalyzed by oxidative enzymes in the ER, cytosol, mitochondria, peroxisomes, and lysosomes. During this process small amounts of partially reduced intermediates are produced in which different numbers

- of electrons have been transferred from  $O_2$ , these include superoxide anion ( $O_2^-$ , one electron), hydrogen peroxide ( $H_2O_2$ , two electrons), and hydroxyl ions ( $\cdot OH$ , three electrons).
2. **Absorption of radiant energy** (e.g., ultraviolet light, x-rays). For example, ionizing radiation can hydrolyze water into  $\cdot OH$  and hydrogen (H) free radicals.
  3. Rapid bursts of ROS are produced in activated leukocytes during **inflammation**. This occurs by a precisely controlled reaction in a plasma membrane multiprotein complex that uses NADPH oxidase for the redox reaction. In addition, some intracellular oxidases (such as xanthine oxidase) generate  $O_2^-$ .
  4. **Enzymatic metabolism of exogenous chemicals or drugs** can generate free radicals that are not ROS but have similar effects (e.g.,  $CCl_4$  can generate  $CCl_3^-$ ).
  5. **Transition metals** such as iron and copper donate or accept free electrons during intracellular reactions and catalyze free radical formation, as in the Fenton reaction ( $H_2O_2 + Fe^{2+} \rightarrow Fe^{3+} + OH + OH^-$ ). Because most of the intracellular free iron is in the ferric ( $Fe^{3+}$ ) state, it must be first reduced to the ferrous ( $Fe^{2+}$ ) form to participate in the Fenton reaction. This reduction can be enhanced by superoxide ( $O_2^-$ ), and thus sources of iron and superoxide may cooperate in oxidative cell damage.
  6. **Nitric oxide (NO)**, an important chemical mediator generated by endothelial cells, macrophages, neurons, and other cell types, can act as a free radical and can also be converted to highly reactive peroxy nitrite anion ( $ONOO^-$ ) as well as  $NO_2$  and  $NO_3^-$ .

(Ref: Robbins & Cotrans – 9<sup>th</sup>, P-47)

**TABLE-- Properties of the Principal Free Radicals Involved in Cell Injury**

Properties	$O_2^-$	$H_2O_2$	$\cdot OH$	$ONOO^-$
<b>MECHANISMS OF PRODUCTION</b>	Incomplete reduction of $O_2$ during oxidative phosphorylation; by phagocyte oxidase in leukocytes	Generated by SOD from $O_2^-$ and by oxidases in peroxisomes	Generated from $H_2O$ by hydrolysis, e.g., by radiation; from $H_2O_2$ by Fenton reaction; from $O_2^-$	Produced by interaction of $O_2^-$ and NO generated by NC synthase in many cell types (endothelial cells, leukocytes, neurons, others)
<b>MECHANISMS OF INACTIVATION</b>	Conversion to $H_2O_2$ and $O_2$ by SOD	Conversion to $H_2O$ and $O_2$ by catalase (peroxisomes), glutathione peroxidase (cytosol, mitochondria)	Conversion to $H_2O$ by glutathione peroxidase	Conversion to $HNO_2$ by peroxiredoxins (cytosol, mitochondria)
<b>PATHOLOGIC EFFECTS</b>	Stimulates production of degradative enzymes in leukocytes and other cells; may directly damage lipids, proteins, DNA; acts close to site of production	Can be converted to $\cdot OH$ and $OCl^-$ , which destroy microbes and cells; can act distant from site of production	Most reactive oxygen-derived free radical; principal ROS responsible for damaging lipids, proteins, and DNA	Damages lipids, proteins, DNA

$HNO_2$ , nitrite;  $H_2O_2$ , hydrogen peroxide; NO, nitric oxide;  $O_2^-$ , superoxide anion;  $OCl^-$ , hypochlorite;  $\cdot OH$ , hydroxyl radical;  $ONOO^-$ , peroxy nitrite; ROS, reactive oxygen species; SOD, superoxide dismutase.

(Ref: Robbins & Cotrans – 9<sup>th</sup>, P-48)

■ Mechanisms of cell injury caused by free radicals:

- Lipid peroxidation of membranes.** In the presence of  $O_2$ , free radicals may cause peroxidation of lipids within plasma and organellar membranes. Oxidative damage is initiated when the double bonds in unsaturated fatty acids of membrane lipids are attacked by  $O_2$ -derived free radicals, particularly by  $\cdot OH$ . The lipid—free radical interactions yield peroxides, which are themselves unstable and reactive, and an autocatalytic chain reaction ensues (called *propagation*), which can result in extensive membrane damage.
- Oxidative modification of proteins.** Free radicals promote oxidation of amino acid side chains, formation of protein-protein cross-linkages (e.g., disulfide bonds), and oxidation of the protein backbone. Oxidative modification of proteins may damage the active sites of enzymes, disrupt the conformation of structural proteins, and enhance proteasomal degradation of unfold or misfold proteins, raising havoc throughout the cell.
- Lesions in DNA.** Free radicals are capable of causing single- and double-strand breaks in DNA, cross-linking of DNA strands, and formation of adducts. Oxidative DNA damage has been implicated in cell aging and in malignant transformation of cells

(Ref: Robbins & Cotran-9<sup>th</sup>, P-49)

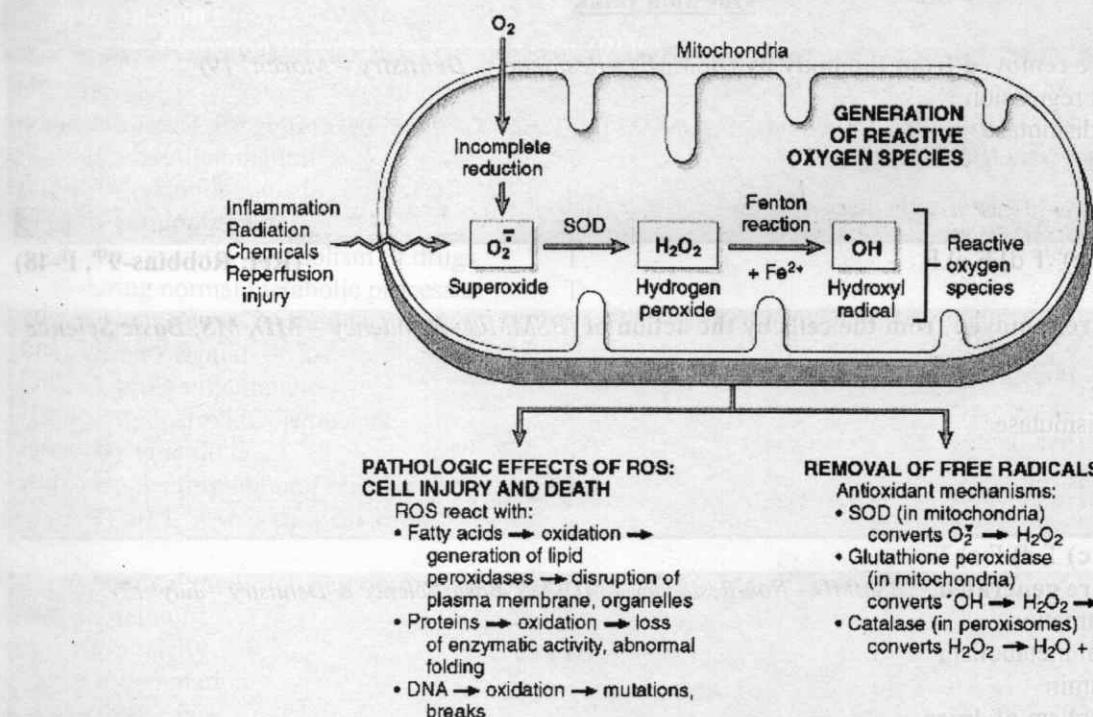


Fig: The role of reactive oxygen species (ROS) in cell injury.  $O_2$  is converted to superoxide ( $O_2^-$ ) by oxidative enzymes in the endoplasmic reticulum (ER), mitochondria, plasma membrane, peroxisomes, and cytosol.  $O_2^-$  is converted to  $H_2O_2$  by dismutation and thence to  $\cdot OH$  by the  $Cu^{2+}/Fe^{2+}$ -catalyzed Fenton reaction.  $H_2O_2$  is also derived directly from oxidases in peroxisomes (not shown). Resultant free radical damage to lipid (peroxidation), proteins, and DNA leads to injury to numerous cellular components. The major antioxidant enzymes are superoxide dismutase (SOD), glutathione peroxidase and catalase.

(Ref: Robbins & Cotran-8<sup>th</sup>, P-21)

**Removal of radical induced injury:**

Free radicals are destroyed by-

- Spontaneous decaying:** Free radicals are inherently unstable and generally decay spontaneously.  $O_2^-$  for example, is unstable and decays (dismutates) spontaneously to  $O_2$  and  $H_2O_2$  in the presence of water.

**2. Nonenzymatic mechanisms:**

i. **Antioxidants:** They either block the initiation of free radical formation or inactivate (e.g. scavenge) free radicals. e.g. vitamin E, vitamin A (retinol), ascorbic acid, glutathione.

ii. **Iron and copper** can catalyze the formation of ROS. The levels of these reactive metals are minimized by binding of the ions to storage and transport proteins (e.g., transferrin, ferritin, lactoferrin, and ceruloplasmin), thereby minimizing the formation of ROS.

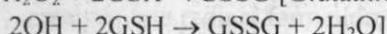
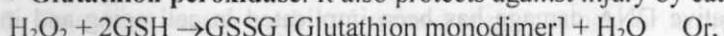
**3. Enzymatic mechanism:**

• **Catalase:** It breaks down  $H_2O_2$

$$2H_2O_2 \rightarrow O_2 + 2H_2O$$

• **Superoxide dismutase:** It converts superoxide ( $O_2^-$ ) to  $H_2O_2$ .

• **Glutathion peroxidase:** It also protects against injury by catalyzing free radical breakdown –



(Ref: Robbins & Cotran-9<sup>th</sup>, P-48)

**Question Bank**

**Q. Free radicals are removed from the body by (BSMMU – Residency - Dentistry – March '19)**

- a) spontaneous regression
- b) superoxide dismutase
- c) ascorbic add
- d) copper
- e) nitric oxide

Ans. a) F b) T c) T d) F e) F

(Ref: Robbins-9<sup>th</sup>, P-48)

**Q. Free radicals are removed from the cells by the action of (BSMMU – Residency – MD, MS, Basic Science – March '18)**

- a) endonuclease
- b) superoxide dismutase
- c) transferrin
- d) vitamin B<sub>12</sub>
- e) glutathione

Ans. a) F b) T c) T d) F e) T

**Q. Free radicals are generated - (BSMMU – Non-Residency – MD, MS, Basic Science & Dentistry – July' 17)**

- a) during inflammation
- b) during normal metabolism
- c) by ceruloplasmin
- d) during metabolism of drugs
- e) by glutathione

Ans. a) T b) T c) F d) T e) F

**Q. Hydrogen peroxide can be neutralized in our body by - (BSMMU – Non-Residency – MD, MS, Basic Science & Dentistry – July' 17)**

- a) myeloperoxidase
- b) catalase
- c) superoxide dismutase
- d) glucose-6-phosphate dehydrogenase
- e) glutathione peroxidase

Ans. a) F b) T c) F d) F e) T

(Ref: Robbins & Cotran-9<sup>th</sup>, P-48)

**Q. Free radicals are generated (BSMMU – Residency - MD, MS, Basic Science - March' 17)**

- a) during inflammation
- b) by glutathione peroxidase
- c) by ceruloplasmin
- d) during metabolism of drugs
- e) during normal metabolic process

**Ans.** a) T b) F c) F d) T e) T

**Q. Hydrogen peroxide can be neutralized by (BSMMU – Residency – MD, MS, Basic science, Dentistry – March' 16)**

- a) superoxide dismutase
- b) catalase
- c) myeloperoxidase
- d) glucose 6-phosphate dehydrogenase
- e) glutathione peroxidase

F  
T  
F  
F  
T

**Q. Free radicals are formed in the body (BSMMU – Non-Residency – MD/MS, Basic science – July' 14)**

- a) by absorption of X-rays
- b) during inflammation
- c) by superoxide dismutases
- d) by vitamin E
- e) by the formation of reactive oxygen species (ROS)

**Ans.** a) T b) T c) F d) F e) T

**Q. Free radicals are generated (BSMMU – Residency - MD/MS, Basic science – March' 14)**

- a) during inflammation
- b) by glutathione
- c) by ceruloplasmin
- d) by enzymatic metabolism of drugs
- e) during normal metabolic processes

T  
F  
F  
T  
T

**Q. Free radicals are formed in the body: (BSMMU – Residency – MD/MS – March'13)**

- a) By absorption of X-rays
- b) During inflammation
- c) By superoxide dismutases
- d) By vitamin E
- e) By the formation of reactive oxygen species

**Ans:** a) T b) T c) F d) F e) T

**Q. Free radical mediated cell damage is seen in: (BSMMU – MS - January, 2010)**

- a) radiation injury
- b) oxygen toxicity
- c) acute inflammation
- d) acute ischaemia
- e) apoptosis

T  
T  
T  
F  
T

**Q. Enzymes that destroy free radicals include: (BSMMU – MS - January, 2010)**

- a) catalase
- b) superoxide dismutase
- c) myeloperoxidase
- d) glutathione peroxidase
- e) cylo-oxygenase

T  
T  
F  
T  
F

**Q. Free radical scavenging enzymes include - (DMC – MD/ MS - January, 2010)**

- a. catalase
- b. protease
- c. superoxide dismutase
- d. glutathione peroxidase
- e. lipase

T  
F  
T  
T  
F

**Q. Generation of free radical occurs in:** (BSMMU - M. Phil, Diploma, July-09)

- |                       |   |
|-----------------------|---|
| a) Nucleus of cells   | F |
| b) Cell membrane      | T |
| c) Reperfusion injury | T |
| d) Necrosed cell      | F |
| e) Radiation          | T |

**Q. Oxygen derived free radicals include** (MD/MS (DMC) – January, 2009)

- |                                      |   |
|--------------------------------------|---|
| a. nitric oxide (NO)                 | F |
| b. hydrogen peroxide ( $H_2O_2$ )    | T |
| c. hydroxyl radical ( $OH^\bullet$ ) | T |
| d super-oxide anion ( $O_2^-$ )      | T |
| e. interleukin -8                    | F |

**Q. Free radicals are formed within cells due to:** (BSMMU – MD/MS- January, 2008)

- |                      |   |
|----------------------|---|
| a) ultraviolet light | T |
| b) vitamin E         | F |
| c) CCl <sub>4</sub>  | T |
| d) copper            | T |
| e) ferritin          | F |

**Q. Free radicals generated in the body are inactivated or destroyed by:** (BSMMU – MD/MS - January, 2008)

- |                  |   |
|------------------|---|
| a) ascorbic acid | T |
| b) acetic acid   | F |
| c) copper        | F |
| d) phosphorus    | F |
| c) catalase      | T |

**Q. Free radical activity is checked by-** (MD/MS (DMC)-08Ja)

- |                           |   |
|---------------------------|---|
| a) ceruloplasmin          | T |
| b) super oxide dismutase  | T |
| c) $\alpha 1$ antitrypsin | F |
| d) NADPH oxidase          | F |
| e) transferrin            | T |

**Q. Free radicals are inactivated by -** (BSMMU - M. Phil, Diploma July-05)

- |                                |   |
|--------------------------------|---|
| A. endogenous oxidase reaction | F |
| B. cytochrome oxidase          | F |
| C. radiant energy              | F |
| D. glutathione peroxidase      | T |
| E. catalase                    | T |

**Q. Free radicals cause cell injury by-** (BSMMU – MD/MS - 05Ja)

- |  |   |
|--|---|
| A. oxidative modification of protein             | T |
| B. peroxidation of lipids within plasma membrane | T |
| C. activation of lysosomal enzyme                | F |
| D. mitochondrial damage                          | T |
| E. cytoskeletal damage                           | F |

**Q. Free radical induced cell injury are mediated by-** (BSMMU-MD/MS - 02Ja)

- |  |   |
|--|---|
| a. Lipid peroxidation of membranes     | T |
| b. Oxidative modifications of proteins | T |
| c. Lesions in RNA                      | F |
| d. Lesions in DNA                      | T |
| e. Increasing cytosolic calcium.       | F |

## Antioxidant

**Q. Substances having antioxidant effects are (BSMMU – Non-Residency – Dentistry – July '19)**

- a) Selenium
- b) beta carotin
- c) vitamin K
- d) vitamin E
- e) thiamine

Ans. a) T   b) T   c) F   d) T   e) F

**Q. The anti-oxidants found in the body are- (MD/MS (DMC)-04Ja)**

- |                  |   |
|------------------|---|
| a) Calmodulin    | F |
| b) Calcitonin.   | F |
| c) Troponin      | F |
| d) Ceruloplasmin | T |
| e) Transferrin   | T |

### HELP LINK:

#### Anti-oxidents found in the body

- |                                  |                         |                 |
|----------------------------------|-------------------------|-----------------|
| • Vitamin A ( $\beta$ -carotene) | • Catalase              | • Glutathione   |
| • Ascorbic acid                  | • Superoxide dismutase  | • Cystine       |
| • Vitamin E                      | • Glutathion peroxidase | • Serum albumin |
|                                  |                         | • Transferrin   |
|                                  |                         | • Ceruloplasmin |
|                                  |                         | • Selenium      |

## CELL INJURY

### Hypoxic cell injury

#### ■ Causes of hypoxic cell injury:

1. inadequate oxygenation of the lungs because of extrinsic reason:	• Deficiency of O <sub>2</sub> in atmosphere
2. Pulmonary disease	• Hypoventilation due to neuromuscular disorder
3. Inadequate transport & delivery of O <sub>2</sub>	• Respiratory failure   • COPD
4. Inadequate tissue capability of using O <sub>2</sub>	<ul style="list-style-type: none"> <li>• Anaemia, abnormal Hb</li> <li>• Circulatory failure</li> <li>• Tissue oedema</li> <li>• CO poisoning</li> <li>• Cyanide poisoning</li> </ul>

**Pathogenesis in ischemic or hypoxic cell injury:** From ischemia or hypoxia, the following events will happen –

A. **Ischemia** → decreased oxidative phosphorylation → decreased ATP. Reduced ATP leads to the followings:

1. The activity of the *plasma membrane energy-dependent sodium pump* (ouabain-sensitive  $\text{Na}^+$ ,  $\text{K}^+$ -ATPase) is reduced → Failure of this active transport system causes sodium to enter and accumulate inside cells and potassium to diffuse out. → The net gain of solute is accompanied by isosmotic gain of water, causing *cell swelling*, and dilation of the Endoplasmic reticulum.
2. *Cellular energy metabolism is altered* → increased *anaerobic glycolysis* → increased accumulation of *lactic acid* and inorganic phosphates hydrolysis of phosphate esters → reduced intracellular pH → decreased activity of many cellular enzymes.

**Fig: Functional and morphologic consequences of decreased intracellular ATP during cell injury**

3. Failure of the  $\text{Ca}^{2+}$  pump leads to influx of  $\text{Ca}^{2+}$ , with damaging effects on numerous cellular components, described below.
4. With prolonged or worsening depletion of ATP, structural disruption of the protein synthetic apparatus occurs, manifested as detachment of ribosomes from the rough ER and dissociation of polysomes, with a consequent *reduction in protein synthesis*.
5. In cells deprived of oxygen or glucose, proteins may become misfolded, and misfolded proteins trigger a cellular reaction called the *unfolded protein response* that may culminate in cell injury and even death. This process is described later in the chapter.
6. Ultimately, there is irreversible damage to mitochondrial and lysosomal membranes, and the cell undergoes *necrosis*.

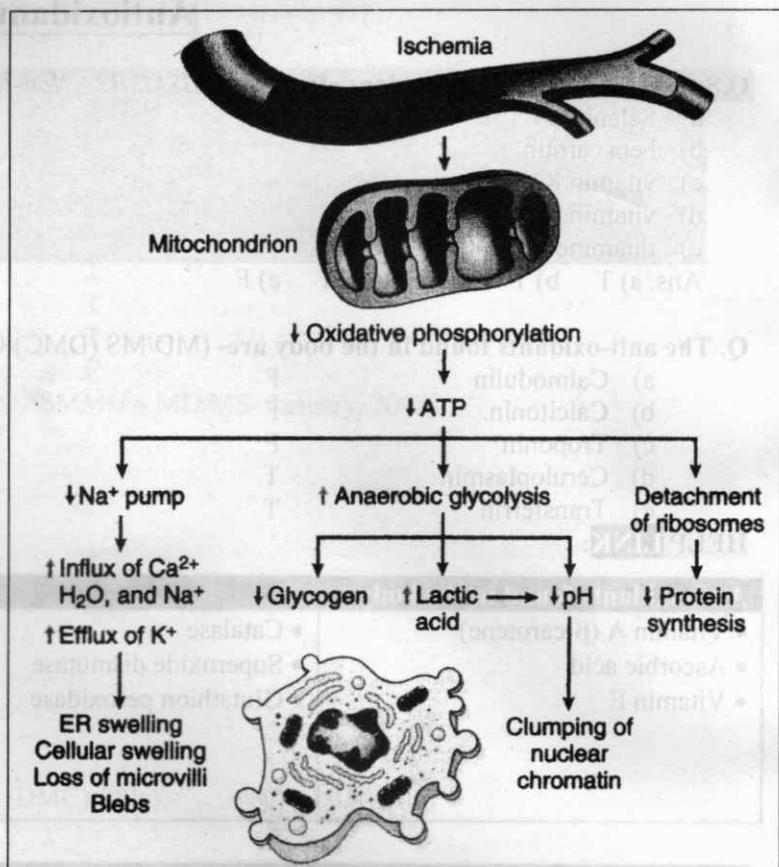
(Ref: Robbins & Cotran-9<sup>th</sup>, P-46)

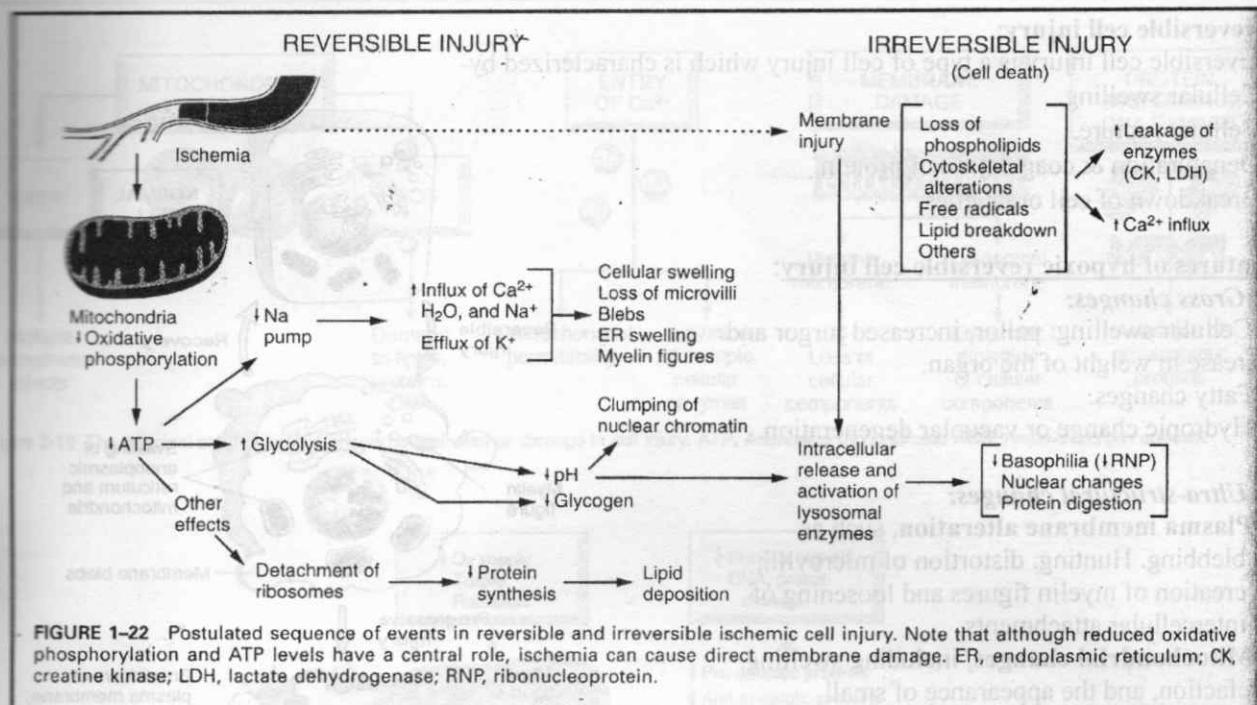
#### **Changes that occur in reversible cell injury:**

A. **Ischemia** → decreased oxidative phosphorylation → decreased ATP. Reduced ATP leads to the followings:  
1 - 6 points (see above)

B. **Ischemia** → Membrane injury that leads to:

1. ↑ Leakage of enzymes (e.g. creatine kinase, lactate dehydrogenase) and ↑ $\text{Ca}^{++}$  influx and their consequences.
2. Intracellular release and activation of lysosomal enzymes that leads to decreased basophilia, nuclear changes and protein digestion.





**FIGURE 1-22** Postulated sequence of events in reversible and irreversible ischemic cell injury. Note that although reduced oxidative phosphorylation and ATP levels have a central role, ischemia can cause direct membrane damage. ER, endoplasmic reticulum; CK, creatine kinase; LDH, lactate dehydrogenase; RNP, ribonucleoprotein.

(Ref: Robbins & Cotran-7<sup>th</sup>, P-24)

### Question Bank

**Q. Hypoxic cell injury leads to (BSMMU – Residency - MD, MS, Basic Science, Dentistry - March '17)**

- a) reduced pH
- b) swelling of the endoplasmic reticulum
- c) reduced lactic acid
- d) influx of potassium
- e) chromatin clumping

**Ans. a) T b) T c) F d) F e) T**

**Q. ATP depletion in cell leads to (BSMMU – Residency - MD, MS, Basic Science- March '17)**

- a) increased intracellular Na<sup>+</sup>
- b) increased intracellular K<sup>+</sup>
- c) increased intracellular pH
- d) increased rate of anaerobic glycolysis
- e) increased intracellular Ca<sup>2+</sup>

**Ans. a) T b) F c) F d) T e) T**

## Reversible & Irreversible cell injury

### Reversible cell injury:

It is a type of cell injury which is characterized by cellular swelling & fatty change.

The hallmarks of reversible injury are-

1. Decreased oxidative phosphorylation.

2. Decreased ATP & cellular swelling caused by changes in ion conc. & water influx. The membranes may be within the cytoplasm (in diaphragm, nucleus, peroxisomes). They are thought to result from an masking of phosphate groups, preventing the entry and intercalation of water between the lamellar stacks of bilayers. At this time the microvilli are usually swollen, as a result of loss of volume control in these cells, the ER remains intact and the entire cell is markedly swollen, with increased concentrations of sodium, and chloride and a decreased concentration of potassium. If oxygen is restored all of these changes are reversible.

#### Irreversible cell injury:

Irreversible cell injury is a type of cell injury which is characterized by-

- Cellular swelling.
  - Cellular rupture.
  - Denaturation & coagulation of protein.
  - Breakdown of cell organelles.

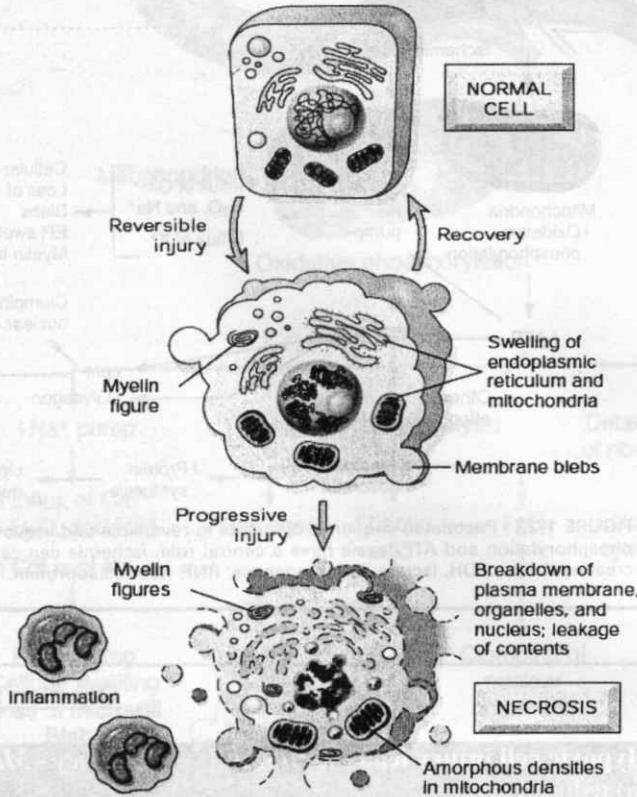
#### **Features of hypoxic reversible cell injury:**

#### **A. Gross changes:**

1. Cellular swelling: pallor, increased turgor and increase in weight of the organ.
  2. Fatty changes.
  3. Hydropic change or vacuolar degeneration.

### **B. Ultra-structural changes:**

- 1. Plasma membrane alteration**, such as blebbing. Hunting, distortion of microvilli, creation of myelin figures and loosening of intercellular attachments.
  - 2. Mitochondrial changes**, including swelling, rarefaction, and the appearance of small phospholipid-rich amorphous densities.
  - 3. Dilation of the endoplasmic reticulum**, with detachment and disaggregation of polysomes.
  - 4. Nuclear alterations**, with disaggregation of granular and fibrillar elements.



**Figure 2-8** Schematic illustration of the morphologic changes in cell injury culminating in necrosis.

(Ref: Robbins-9<sup>th</sup>, P-40,41)

#### **Features of hypoxic irreversible cell injury:**

1. Increased eosinophilia of cells.
  2. More glassy homogeneous appearance than do normal cells, mainly as a result of the loss of glycogen particles.
  3. Cytoskeletal alteration.
  4. Lysis of endoplasmic reticulum (ER).
  5. Rupture of lysosome and autolysis.
  6. Lipid breakdown.
  7. Appearance of myelin figures
  8. Nuclear changes-
    - a) Pyknosis
    - b) Karyorrhexis
    - c) Karyolysis
  9. Protein digestion.

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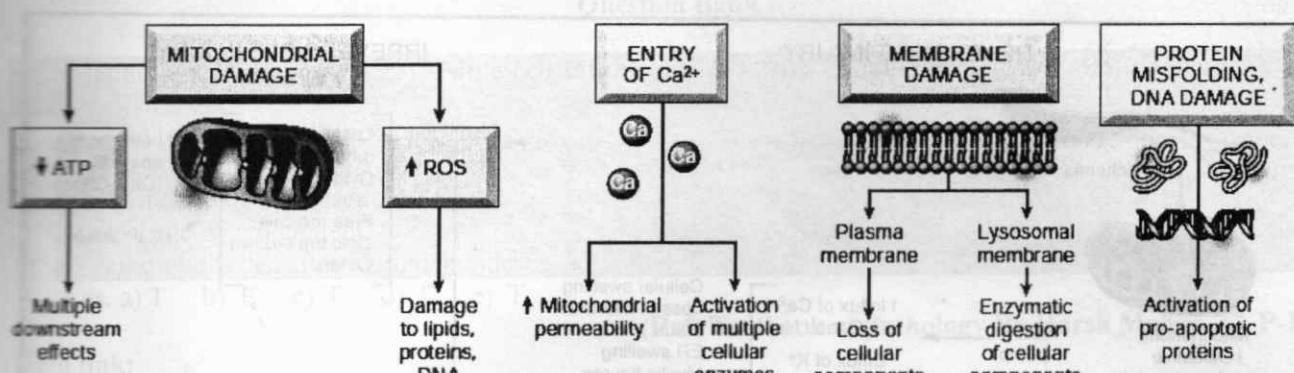


Figure 2-16 The principal biochemical mechanisms and sites of damage in cell injury. ATP, Adenosine triphosphate; ROS, reactive oxygen species.

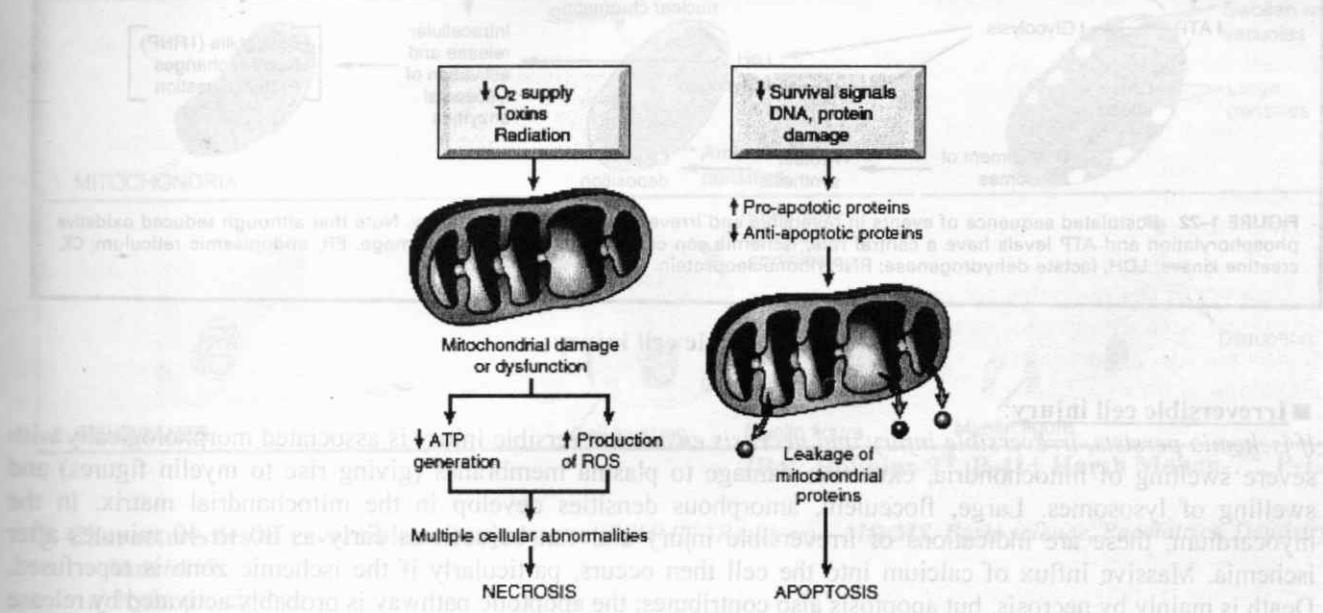


Fig: Role of mitochondria in cell injury and death. Mitochondria are affected by a variety of injurious stimuli and their abnormalities lead to necrosis or apoptosis. ATP, Adenosine triphosphate; ROS, reactive oxygen species.

### Mechanisms of Ischemic Cell Injury:

#### ■ Reversible cell injury:

In ischaemia, as the oxygen tension within the cell decreases, there is loss of oxidative phosphorylation and decreased generation of ATP. The depletion of ATP results in failure of the sodium pump, with loss of potassium, influx of sodium and water, and cell swelling. There is also influx of  $\text{Ca}^{2+}$ , with its many deleterious effects. There is progressive loss of glycogen and decreased protein synthesis. The functional consequences may be severe at this stage. For instance, heart muscle ceases to contract within 60 seconds of coronary occlusion. Note, however, that loss of contractility does not mean cell death. If hypoxia continues, worsening ATP depletion causes further deterioration. The cytoskeleton disperses, resulting in the loss of ultrastructural features such as microvilli and the formation of "blebs" at the cell surface. "Myelin figures," derived from degenerating cellular membranes, may be seen within the cytoplasm (in autophagic vacuoles) or extracellularly. They are thought to result from unmasking of phosphatide groups, promoting the uptake and intercalation of water between the lamellar stacks of membranes. At this time the mitochondria are usually swollen, as a result of loss of volume control in these organelles; the ER remains dilated; and the entire cell is markedly swollen, with increased concentrations of water, sodium, and chloride and a decreased concentration of potassium. *If oxygen is restored, all of these disturbances are reversible.*

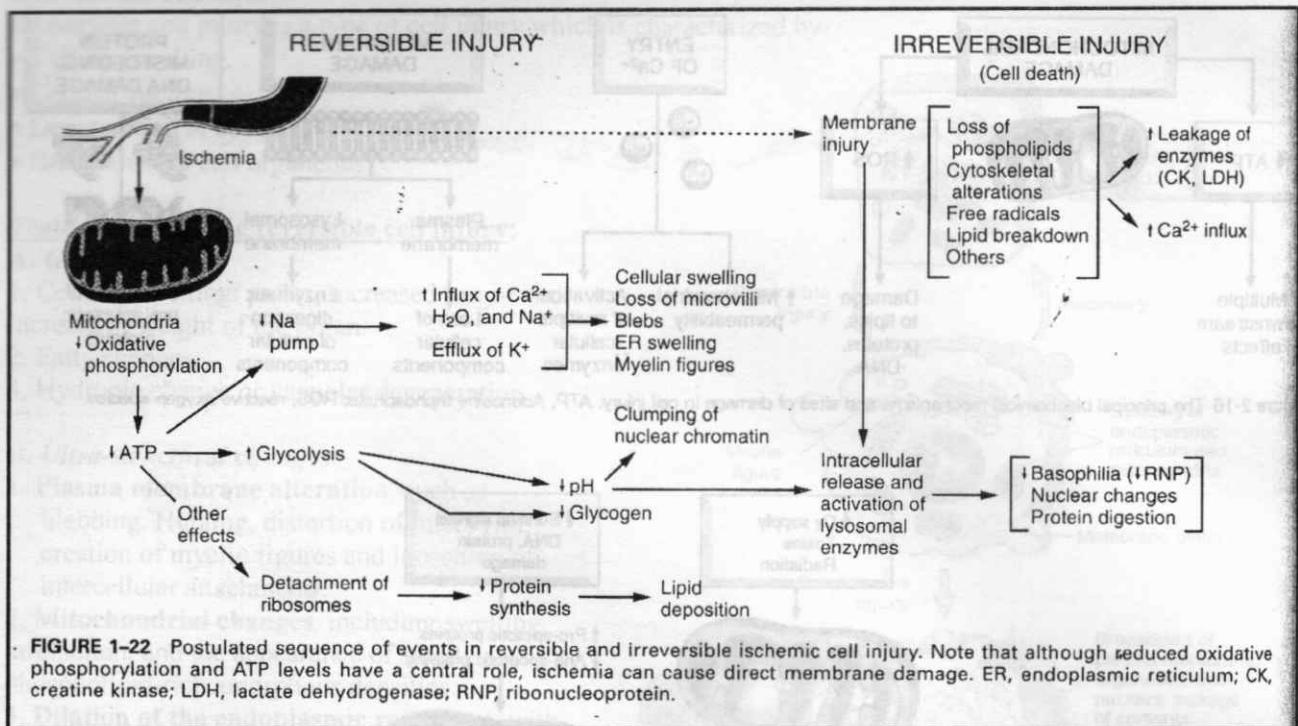


Fig: Ischemic cell injury

### ■ Irreversible cell injury:

If ischemia persists, irreversible injury and necrosis ensue. Irreversible injury is associated morphologically with severe swelling of mitochondria, extensive damage to plasma membranes (giving rise to myelin figures) and swelling of lysosomes. Large, flocculent, amorphous densities develop in the mitochondrial matrix. In the myocardium, these are indications of irreversible injury and can be seen as early as 30 to 40 minutes after ischemia. Massive influx of calcium into the cell then occurs, particularly if the ischemic zone is reperfused. Death is mainly by necrosis, but apoptosis also contributes; the apoptotic pathway is probably activated by release of pro-apoptotic molecules from leaky mitochondria. The cell's components are progressively degraded, and there is wide spread leakage of cellular enzymes into the extracellular space and, conversely, entry of extracellular macromolecules from the interstitial space into the dying cells. Finally, the dead cells may become replaced by large masses composed of phospholipids in the form of myelin figures.

These are then either phagocytosed by leukocytes or degraded further into fatty acids. Calcification of such fatty acid residues may occur, with the formation of calcium soaps.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-50-51)

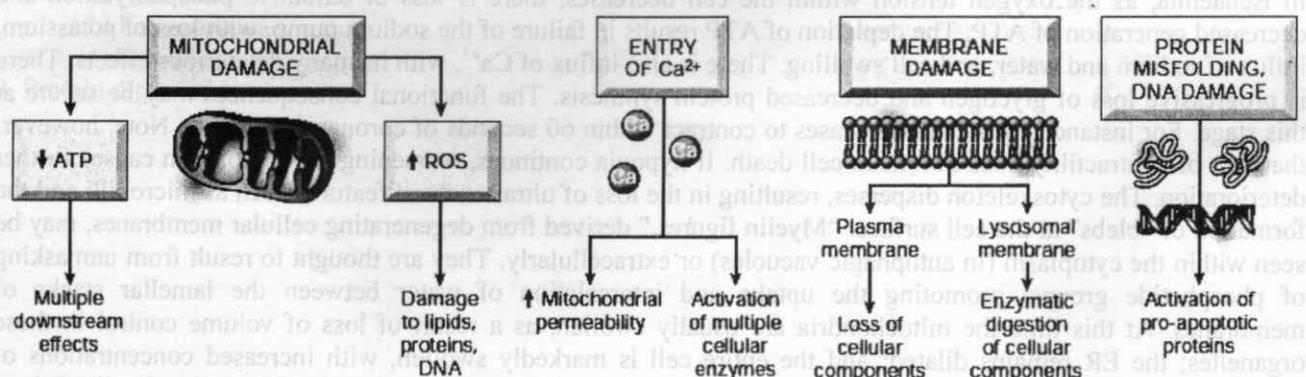


Figure 2-16 The principal biochemical mechanisms and sites of damage in cell injury. ATP, Adenosine triphosphate; ROS, reactive oxygen species.

**Question Bank**

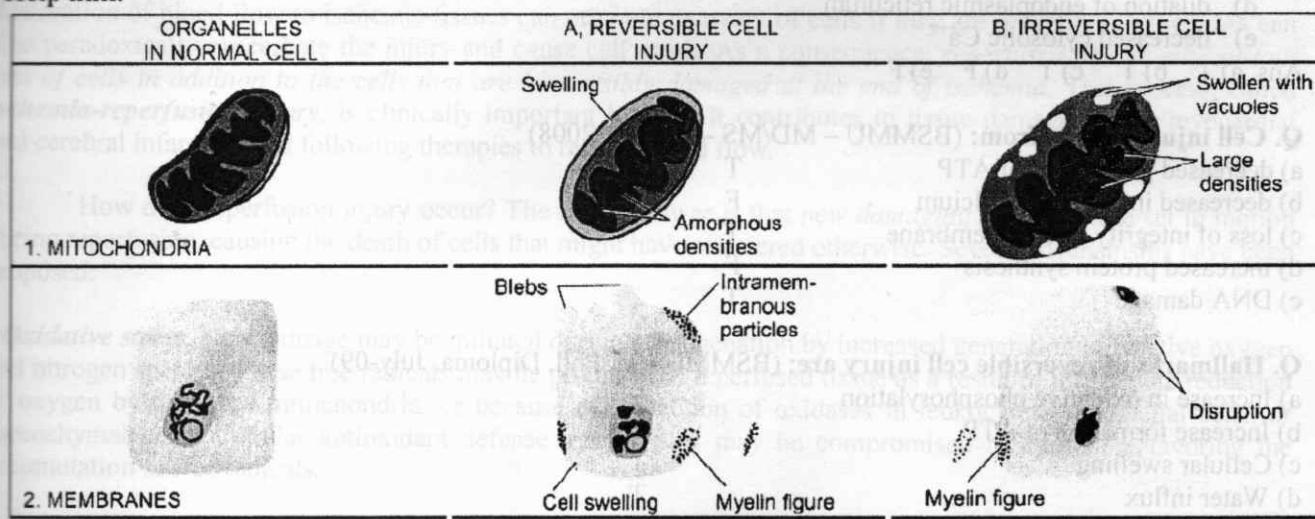
**Q. Morphological changes in reversible cell injury are (BSMMU – Non-Residency – MD, MS, Paediatrics, Basic Science – July' 19)**

- a) swelling of endoplasmic reticulum
- b) breakdown of plasma membrane
- c) formation of lipid vacuoles
- d) leakage of cell contents
- e) amorphous densities in mitochondria

Ans. a) T b) F c) F d) F e) T

(Ref: Textbook of Pathology By Harsh Mohan-7<sup>th</sup>, P-12)

**Help link:**



(Ref: Robbins-9<sup>th</sup>, P-41+ Harsh Mohan-7<sup>th</sup>, P-12)

**Q. Characteristics of reversible cell injury are (BSMMU – Residency - MD/MS, Basic science, Paediatrics, Dentistry – March' 19)**

- a) hydropic change
- b) increased basophilia of cytoplasm
- c) breakdown of plasma membrane
- d) fatty change
- e) intracytoplasmic myelin figures

Ans: a) T b) F c) F d) T e) T

**Q. Ultrastructural changes of reversible cell injury include (BSMMU – Residency – MD, MS, Basic Science – March' 18)**

- a) loss of microvilli in plasma membrane
- b) detachment of polysomes from endoplasmic reticulum
- c) condensation of nuclear chromatin
- d) appearance of intracytoplasmic myelin figures
- e) appearance of translucent areas in mitochondria

Ans. a) T b) T c) F d) T e) F (amorphous density)

**Q. Pathogenesis of reversible cell injury includes (BSMMU – Non-Residency – MD, MS, Basic science – July' 16)**

- a) decreased generation of cellular ATP T
- b) intracellular acidosis T
- c) reduced protein synthesis T
- d) cytoskeletal damage F
- e) karyorrhexis F

**Q. In irreversible cell injury there is (BSMMU – Residency – MD, MS, Basic science, Dentistry – March' 16)**

- |                                       |   |
|---------------------------------------|---|
| a) ATP depletion                      | T |
| b) decreased protein synthesis        | F |
| c) increased pH                       | F |
| d) cell membrane damage               | T |
| e) shrinkage of endoplasmic reticulum | F |

**Q. Irreversible cell injury is associated with (BSMMU – Non-Residency - MD/MS, Basic science – 13Ju)**

- |   |
|---|
| a) extensive damage to cellular membranes |
| b) swelling of lysosomes                  |
| c) vacuolization of mitochondria          |
| d) dilation of endoplasmic reticulum      |
| e) decreased cytosolic $\text{Ca}^{++}$   |

Ans. a) T b) T c) T d) F e) F

**Q. Cell injury results from: (BSMMU – MD/MS - January, 2008)**

- |                                       |   |
|---------------------------------------|---|
| a) decreased production of ATP        | T |
| b) decreased intracellular calcium    | F |
| c) loss of integrity of cell membrane | T |
| d) increased protein synthesis        | F |
| e) DNA damage                         | T |

**Q. Hallmarks of reversible cell injury are: (BSMMU - M. Phil, Diploma, July-09)**

- |  |   |
|--|---|
| a) Increase in oxidative phosphorylation   | F |
| b) Increase formation of ATP               | F |
| c) Cellular swelling                       | T |
| d) Water influx                            | T |
| e) Amorphous densities in the mitochondria | F |

**Q. In reversible cell injury, there is: (BSMMU – MD/MS - January, 2008)**

- |   |   |
|---|---|
| a) increased glycolysis                   | T |
| b) decreased protein synthesis            | T |
| c) increased pH                           | F |
| d) increased intracellular $\text{K}^{+}$ | F |
| e) loss of microvilli                     | T |

**Q. Indications of irreversible injury are: (BSMMU – MD/MS - 05Ja)**

- |  |                                    |
|--|------------------------------------|
| A. severe vacuolization of mitochondria  | T                                  |
| B. extensive damage to plasma membranes  | T                                  |
| C. swelling of the endoplasmic reticulum | F ( <i>Swelling of lysosomes</i> ) |
| D. Mitochondrial dysfunction             | T                                  |
| E. Clumping of nuclear chromatin         | F                                  |

**Q. Reversible cell injury is characterized by: (MD/MS (DMC)-03Ja)**

- |                                  |                                   |
|----------------------------------|-----------------------------------|
| a) Myelin figures                | T [Ref. Robbins-7 <sup>th</sup> ] |
| b) Clumping of nuclear chromatin | T                                 |
| c) Increased Ca in mitochondria. | F                                 |
| d) Karyorrhexis                  | F                                 |
| e) Lipid deposition              | T                                 |

## ISCHEMIA-REPERFUSION INJURY

**Q.** Ischemic reperfusion injury is caused by (BSMMU – Residency – MD, MS, Basic Science – March' 18)

- a) restoration of blood flow by thrombolysis
- b) toxic effect of hemoglobin from breakdown of extravasated red blood cells
- c) influx of sodium into the cells
- d) intracellular calcium overload
- e) complement activation by IgM

Ans. a) T b) F c) F d) T e) T

**HELP LINK:**

### ISCHEMIA-REPERFUSION INJURY:

Restoration of blood flow to ischemic tissues can promote recovery of cells if they are reversibly injured, but can also paradoxically exacerbate the injury and cause cell death. As a consequence, *reperfused tissues may sustain loss of cells in addition to the cells that are irreversibly damaged at the end of ischemia*. This process, called **ischemia-reperfusion injury**, is clinically important because it contributes to tissue damage during myocardial and cerebral infarction and following therapies to restore blood flow.

How does reperfusion injury occur? The likely answer is that *new damaging processes* are set in motion during reperfusion, causing the death of cells that might have recovered otherwise. Several mechanisms have been proposed:

• **Oxidative stress.** New damage may be initiated during reoxygenation by increased generation of reactive oxygen and nitrogen species. These free radicals may be produced in reperfused tissue as a result of incomplete reduction of oxygen by damaged mitochondria, or because of the action of oxidases in leukocytes, endothelial cells, or parenchymal cells. Cellular antioxidant defense mechanisms may be compromised by ischemia, favoring the accumulation of free radicals.

• **Intracellular calcium overload.** As mentioned earlier, intracellular and mitochondrial calcium overload begins during acute ischemia; it is exacerbated during reperfusion due to influx of calcium resulting from cell membrane damage and ROS mediated injury to sarcoplasmic reticulum. Calcium overload favors opening of the mitochondrial permeability transition pore with resultant depletion of ATP. This in turn causes further cell injury.

• **Inflammation.** Ischemic injury is associated with inflammation as a result of “danger signals” released from dead cells, cytokines secreted by resident immune cells such as macrophages, and increased expression of adhesion molecules by hypoxic parenchymal and endothelial cells, all of which act to recruit circulating neutrophils to reperfused tissue. The inflammation causes additional tissue injury. The importance of neutrophil influx in reperfusion injury has been demonstrated experimentally by the salutary effects of treatment with antibodies that block cytokines or adhesion molecules and thereby reduce neutrophil extravasation.

• Activation of the **complement system** may contribute to ischemia-reperfusion injury. Some IgM antibodies have a propensity to deposit in ischemic tissues, for unknown reasons, and when blood flow is resumed, complement proteins bind to the deposited antibodies, are activated, and cause more cell injury and inflammation.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-51)

**Q. Restoration of blood flow to an area of ischemia:** (BSMMU – MS - January, 2010)

- a) will result in recovery of irreversibly injured cells
- b) produce reperfusion injury through free radicals
- c) cause further cell death exclusively by apoptosis
- d) prevent further tissue damage by necrosis up to 48 hours
- e) may produce tissue damage through IgM mediated complement activation

Ans. a) F b) T c) F d) F e) T

## NECROSIS

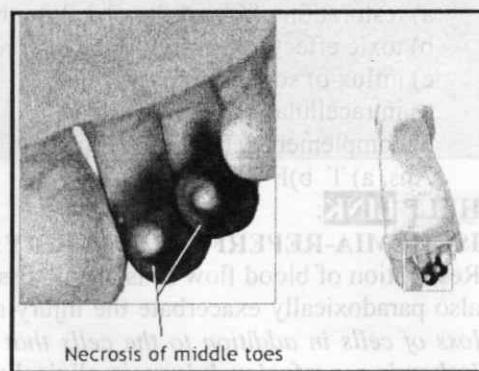
■ **Definition:** Necrosis refers to a spectrum of morphologic changes that follows cell death in living tissue, largely resulting from the progressive degradative action of enzymes on the lethally injured cell.

### Features:

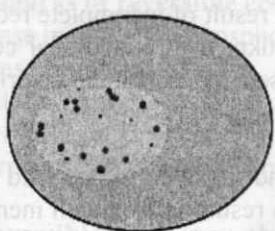
- Denaturation of intracellular protein
- Enzymatic digestion of lethally injured cells.
- Membrane damage severe
- Contents leak and causes surrounding inflammatory reaction
- Always pathologic process

### Morphology:

1. Increased eosinophilia
2. Moth-eaten---replaced by myelin figures.
3. Loss of cytoplasmic RNA
4. Cells show glassy homogenous appearance
5. Nuclear changes: (**Hallmark**)
  - a. Pyknosis- nuclear shrinkage & increase basophilia
  - b. Karyorrhexis- fragmentation after passes of time nucleus totally disappears.
  - c. Karyolysis- loss of DNA, degradation by endonucleases

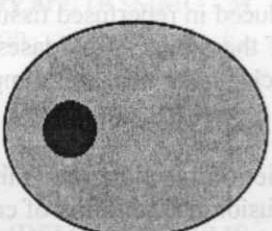


**KARYOLYSIS**



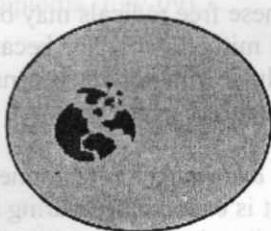
**Nuclear fading**

**PYKNOSIS**



**Nuclear shrinkage**

**KARYORRHEXIS**



**Nuclear fragmentation**

**Nuclear dissolution**

**ANUCLEAR NECROTIC CELL**

### ■ Classification / types of necrosis with example:

#### Basic types:

1. **Coagulative necrosis:** e.g.- ischaemic necrosis of heart (myocardial infarction), kidney, liver, adrenal gland and other solid organs.
2. **Liquefactive/ colligative necrosis:** e.g.- Abscess, boil and ischaemic necrosis of brain tissue.

**Special types:**

1. **Caseous necrosis:** e.g.- granuloma of tuberculosis.
2. **Fat necrosis:**
  - a) Enzymatic fat necrosis: e.g.- enzymatic fat necrosis of pancreas and omental tissue.
  - b) Traumatic fat necrosis: e.g.- traumatic fat necrosis of breast.
3. **Gangrenous necrosis:** e.g.- any necrosis with superadded putrefaction.
4. **Fibrinoid necrosis:** e.g.- Acute rheumatic fever, rheumatoid arthritis, systemic lupus erythematosus (SLE) etc.
5. **Necrosis of muscle:** e.g.- Zenker's degeneration.

(Ref: Khaleque's pathology)

#### ■ Description:

**COAGULATIVE NECROSIS:** This results primarily from denaturation of structural & enzymatic proteins due to increasing intracellular acidosis of coagulated cell and is maintained at least some days. The basic cellular shape, outline & architecture is preserved. The cell takes acidophilic stain.

#### Examples:

- i. Ischaemia caused by obstruction in a vessel in all organs except brain. e. g. Infarct of heart, kidney, spleen. In MI, cells become acidophilic, coagulated & anucleated. The necrotic cells are removed by fragmentation & phagocytosis of the cellular debris by macrophages & by the action of proteolytic lysosomal enzymes.
- ii. Gumma of tertiary syphilis.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-43)

**LIQUEFACTIVE NECROSIS:** It is characterized by digestion of the dead cells, resulting in transformation of the tissue into a liquid viscous mass. **It is seen in focal bacterial or, occasionally, fungal infections**, because microbes stimulate the accumulation of leukocytes and the liberation of enzymes from these cells. The necrotic material is frequently creamy yellow because of the presence of dead leukocytes and is called **pus**.

#### Example:

- i. Suppurative inflammation
- ii. Hypoxic death of cells within brain – Infarction of brain.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-43)

#### ■ Clinical examples of liquefactive necrosis:

1. Abscess
2. Ischaemic necrosis of brain tissue.

**GANGRENOUS NECROSIS** is not a specific pattern of cell death, but the term is commonly used in clinical practice. It is usually applied to a limb, generally the lower leg, that has lost its blood supply and has undergone necrosis (typically coagulative necrosis) involving multiple tissue planes. When bacterial infection is superimposed there is more liquefactive necrosis because of the actions of degradative enzymes in the bacteria and the attracted leukocytes (giving rise to so-called **wet gangrene**).

(Ref: Robbins & Cotran-9<sup>th</sup>, P-43)

**CASEOUS NECROSIS:** It is a distinctive form of coagulative necrosis. It occurs most commonly in foci of tuberculous infection. The term "caseous" (cheese-like) is derived from the friable white appearance of the area of necrosis. Microscopically, the necrotic area appears as a collection of fragmented or lysed cells and amorphous granular debris enclosed within a distinctive inflammatory border; this appearance is characteristic of a focus of inflammation known as a **granuloma**. The tissue architecture is lost & the cell outline is not preserved.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-43)

#### **FAT NECROSIS:** It is of two types -

- a) **Enzymatic fat necrosis:** e.g.- enzymatic fat necrosis of pancreas and omental tissue.  
It refers to focal areas of fat destruction, typically resulting from release of activated pancreatic lipases into the substance of the pancreas and the peritoneal cavity. This occurs in the calamitous abdominal emergency known as acute pancreatitis. In this disorder pancreatic enzymes leak out of acinar cells and liquefy the membranes of fat cells in the peritoneum. The released lipases split the triglyceride esters contained within fat cells. The fatty acids,

so derived, combine with calcium to produce grossly visible chalky-white areas (fat saponification), which enable the surgeon and the pathologist to identify the lesions. On histologic examination the necrosis takes the form of foci of shadowy outlines of necrotic fat cells, with basophilic calcium deposits, surrounded by an inflammatory reaction.

b) **Traumatic fat necrosis:** e.g.- traumatic fat necrosis of breast.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-43,44)

**FIBRINOID NECROSIS** is a special form of necrosis usually seen in immune reactions involving blood vessels. This pattern of necrosis typically occurs when complexes of antigens and antibodies are deposited in the walls of arteries. Deposits of these "immune complexes," together with fibrin that has leaked out of vessels, result in a bright pink and amorphous appearance in H&E stains, called "fibrinoid" (fibrin-like) by pathologists.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-44)

### Question bank

**Q. Features of necrosis are (BSMMU – Residency - Dentistry – March' 19)**

- a) swelling of cells
- b) shrinkage of endoplasmic reticulum
- c) karyorrhexis
- d) disrupted cell membrane
- e) absence of inflammation

Ans. a) T b) F c) T d) T e) F (presence of inflammatory cells in and around the necrosis)

(Ref. Robbins-9<sup>th</sup>, P-40)

**Q. Liquefactive necrosis occurs in (BSMMU – Residency – MD, MS, Basic Science, Dentistry – March' 18)**

- a) fungal infection
- b) bacterial infection
- c) hypoxic injury in brain
- d) ischemic injury in ovary
- e) acute inflammation of pancreas

Ans. a) T b) T c) T d) F e) F

**Q. Caseation necrosis (BSMMU – Residency – MD, MS, Basic science, Dentistry – March' 16)**

- a) is a distinctive form of coagulation necrosis
- b) is encountered most often in tuberculosis
- c) appears cheesy white on naked eye
- d) implies preservation of basic outline of necrosed cells
- e) is characteristic of focal fungal infection

Ans. a) T (Ref: Prof. Khaleque) b) T c) T d) F e) F

**Q. Liquefactive necrosis is seen in (BSMMU – Non-Residency – MD, MS, Basic science, Dentistry – July' 15)**

- |                          |   |
|--------------------------|---|
| a) brain hypoxia         | T |
| b) tubercular lymph node | F |
| c) abscess               | T |
| d) ulcer                 | F |
| e) myocardial infarction | F |

**Q. Gangrenous necrosis (BSMMU – Non-Residency – MD/MS, Basic science – July' 14)**

- a) is a combination of coagulative and liquefaction necrosis
- b) occurs in gut
- c) looks like cheese on naked eye
- d) occur in lower limb in diabetic patient
- e) usually surrounded by granuloma

Ans. a) T b) T c) F d) T e) F

**Q. Gangrenous necrosis (BSMMU –Residency - MD/MS, Basic science – March' 14)**

- |  |   |
|--|---|
| a) is a term used in clinical practice     | T (Ref: Robbins-9 <sup>th</sup> , P-43) |
| b) may occur in gut                        | T                                       |
| c) is a specific pattern of cell death     | F (Ref: Robbins-9 <sup>th</sup> , P-43) |
| d) typically involves the brain            | F                                       |
| e) is superimposed by bacterial infections | T                                       |

**Q. Liquefactive necrosis occurs in (BSMMU – Non-Residency - MD/MS, Basic science – 13Ju)**

- |                          |                |
|--------------------------|----------------|
| a) fungal infection      | T (occasional) |
| b) acute pancreatitis    | F              |
| c) bacterial infections  | T              |
| d) hypoxia in brain      | T              |
| e) myocardial infarction | F              |

**Q. Liquefactive necrosis is seen in: (BSMMU – Residency – MD/MS – March'13)**

- |                                |  |
|--------------------------------|--|
| a) Abscess cavity              |  |
| b) Centre of a granuloma       |  |
| c) Wet gangrene                |  |
| d) Oxygen deprivation of heart |  |
| e) Oxygen deprivation of brain |  |

Ans : a) T b) F c) T d) F e) T

**Q. Enzymatic fat necrosis (BSMMU – MD/MS (Residency) – January, 2011)**

- |  |   |
|--|---|
| a) is seen in breast                         | F |
| b) caused by release of lipase               | T |
| c) induces calcium deposition                | T |
| d) is common in fatty persons                | T |
| e) completely eliminates tissue architecture | T |

**Q. Necrosis in a solid organ due to ischaemia : (BSMMU – MD/MS (Residency) – January, 2011)**

- |                                      |   |
|--------------------------------------|---|
| a) is called infarction              | T |
| b) is dusky red in color             | F |
| c) is coagulative in nature          | T |
| d) is reversed in nature             | F |
| e) does not produce any inflammation | F |

*Fig: Apoptosis*

**Q. Coagulative necrosis of an intra-abdominal organ - (BSMMU – MD/MS- January, 2009)**

- |   |   |
|---|---|
| a) is a sequela of acute pancreatitis                     | F |
| b) is indicative of vascular obstruction                  | T |
| c) is commonly caused by coagulase positive staphylococci | F |
| d) is always pale   | F |
| e) can be recognized by microscopic examination           | T |

**Q. Coagulative necrosis is seen in the following conditions (BSMMU - M. Phil, Diploma, July-04)**

- |                          |   |
|--------------------------|---|
| A. Brain in ischemia     | F |
| B. Myocardial infarction | T |
| C. Within an abscess     | F |
| D. Intestine in volvulus | F |
| E. Centre of a granuloma | F |

**Q. Caseous necrosis occurs in - (MD/MS (DMC)-08Ja)**

- a) tuberculoid leprosy F
- b) erythema nodosum F
- c) tuberculosis verrucosa cutis T
- d) sarcoidosis F
- e) erythema induratum F

**HELP LINK:**

Disease	Tissue reaction
TB	i. Noncaseating tubercle (granuloma prototype): a focus of epithelioid cells, rimmed by fibroblasts, lymphocytes, histiocytes, occasional Langhans giant cell; acid-fast bacilli. ii. Caseating tubercle: central amorphous granular debris, loss of all cellular detail; acid-fast bacilli.
Leprosy	Acid fast bacilli in macrophages; non-caseating granuloma
Syphilis	<b>Gumma:</b> microscopic to grossly visible lesion, enclosing wall of histiocytes; plasma cell infiltrate, center cells are necrotic without loss of cellular outline.
Cat-scratch disease	Rounded or stellate granuloma containing central granular debris and recognizable neutrophils; giant cells uncommon.

[Soft tubercle = caseating tubercle of TB.]

(Ref: Robbins & Cotran-7<sup>th</sup>, P-83)

**Q. Caseation commonly occurs in- (BSMMU-MD - 02J)**

- a) Actinomycosis F
- b) Gas gangrene F
- c) Sarcoidosis F
- d) Staphylococcal infections F
- e) TB. T

**Q. Caseation commonly occurs in: (MD/MS (DMC) – 02Ja)**

- A. Actinomycosis. F
- B. Gas gangrene. F
- C. Sarcoidosis. F
- D. Staphylococcal infections. F
- E. Tuberculosis. T

- Q. Liquefactive necrosis is seen in:  
 A. Malaria  
 B. tubercular lymph nodes  
 C. abscess  
 D. ulcer  
 E. myocardial infarction



## APOPTOSIS

**Definition:** *Apoptosis* is a pathway of cell death that is induced by a tightly regulated suicide program in which cells destined to die activate enzymes that degrade the cells' own nuclear DNA and nuclear and cytoplasmic proteins.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-52)

Or, Apoptosis is a morphological pattern of internally programmed cell death.

### ■ Causes of Apoptosis:

#### A. Apoptosis in Physiologic conditions:

1. *The programmed destruction of cells during embryogenesis*, including implantation, organogenesis, developmental involution, and metamorphosis.
2. *Involution of hormone-dependent tissues upon hormone withdrawal*, such as endometrial cell breakdown during the menstrual cycle, ovarian follicular atresia in menopause, the regression of the lactating breast after weaning, and prostatic atrophy after castration.
3. *Cell loss in proliferating cell populations*, such as immature lymphocytes in the bone marrow and thymus that fail to express useful antigen receptors, B lymphocytes in germinal centers, and epithelial cells in intestinal crypts, so as to maintain a constant number (*homeostasis*).
4. *Elimination of potentially harmful self-reactive lymphocytes*, either before or after they have completed their maturation, so as to prevent reactions against one's own tissues.
5. *Death of host cells*, such as neutrophils in an *acute inflammatory response*, and lymphocytes at the end of an *immune response*. In these situations cells undergo apoptosis because they are deprived of necessary survival signals, such as growth factors.

#### B. Apoptosis in Pathologic conditions:

1. **DNA damage.** Radiation, cytotoxic anticancer drugs, and hypoxia can damage DNA, either directly or via production of free radicals. If repair mechanisms cannot cope with the injury, the cell triggers intrinsic mechanisms that induce apoptosis. In these situations elimination of the cell may be a better alternative than risking mutations in the damaged DNA, which may result in malignant transformation.
2. **Accumulation of misfolded proteins.** Improperly folded proteins may arise because of mutations in the genes encoding these proteins or because of extrinsic factors, such as damage caused by free radicals. Excessive accumulation of these proteins in the ER leads to a condition called *ER stress*, which culminates in apoptotic cell death. Apoptosis caused by the accumulation of misfolded proteins has been invoked as the basis of several degenerative diseases of the central nervous system and other organs.

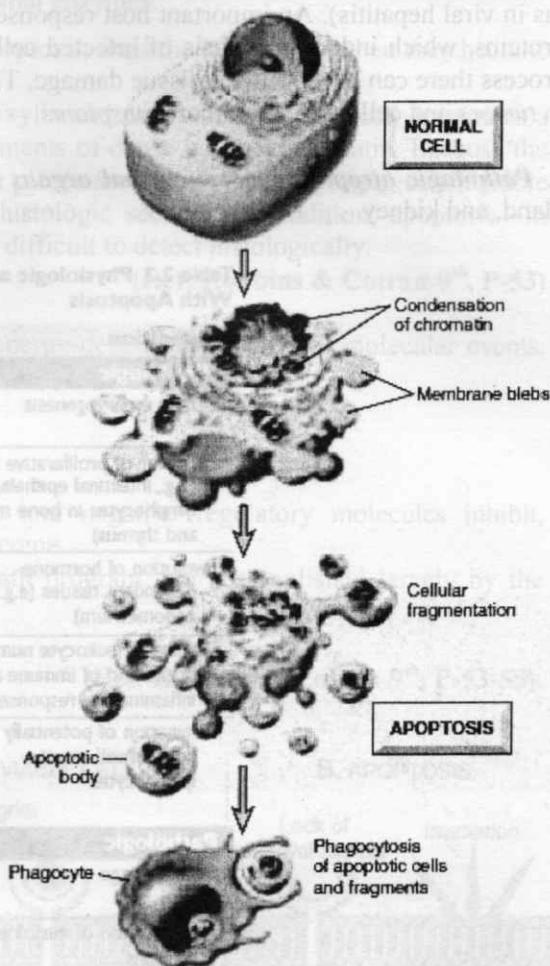


Fig: Apoptosis

3. **Cell death in certain infections**, particularly viral infections, in which loss of infected cells is largely due to apoptosis that may be induced by the virus (as in adenovirus and HIV infections) or by the host immune response (as in viral hepatitis). An important host response to viruses consists of cytotoxic T lymphocytes specific for viral proteins, which induce apoptosis of infected cells in an attempt to eliminate reservoirs of infection. During this process there can be significant tissue damage. The same T-cell-mediated mechanism is responsible for cell death in tumors and cellular rejection of transplants.

4. **Pathologic atrophy in parenchymal organs after duct obstruction**, such as occurs in the pancreas, parotid gland, and kidney.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-52-53)

**Table 2.2 Physiologic and Pathologic Conditions Associated With Apoptosis**

Condition	Mechanism of Apoptosis
<b>Physiologic</b>	
During embryogenesis	Loss of growth factor signaling (presumed mechanism)
Turnover of proliferative tissues (e.g., intestinal epithelium, lymphocytes in bone marrow, and thymus)	Loss of growth factor signaling (presumed mechanism)
Involution of hormone-dependent tissues (e.g., endometrium)	Decreased hormone levels lead to reduced survival signals
Decline of leukocyte numbers at the end of immune and inflammatory responses	Loss of survival signals as stimulus for leukocyte activation is eliminated
Elimination of potentially harmful self-reactive lymphocytes	Strong recognition of self antigens induces apoptosis by both the mitochondrial and death receptor pathways
<b>Pathologic</b>	
DNA damage	Activation of proapoptotic proteins by BH3-only sensors
Accumulation of misfolded proteins	Activation of proapoptotic proteins by BH3-only sensors, possibly direct activation of caspases
Infections, especially certain viral infections	Activation of the mitochondrial pathway by viral proteins Killing of infected cells by cytotoxic T lymphocytes, which activate caspases

(Ref: Robbin's Basic Pathology-1<sup>th</sup>, P-38)

### Morphology:

The following morphologic features, some best seen with the electron microscope, characterize cells undergoing apoptosis.

1. **Cell shrinkage.** The cell is smaller in size; the cytoplasm is dense; and the organelles, though relatively normal, are more tightly packed. (Recall that in other forms of cell injury, an early feature is cell swelling, not shrinkage.)
2. **Chromatin condensation.** This is the most characteristic feature of apoptosis. The chromatin aggregates peripherally, under the nuclear membrane, into dense masses of various shapes and sizes. The nucleus itself may break up, producing two or more fragments.
3. **Formation of cytoplasmic blebs and apoptotic bodies.** The apoptotic cell first shows extensive surface blebbing, then undergoes fragmentation into membrane-bound apoptotic bodies composed of cytoplasm and tightly packed organelles, with or without nuclear fragments.

4. **Phagocytosis of apoptotic cells or cell bodies, usually by macrophages.** The apoptotic bodies are rapidly ingested by phagocytes and degraded by the phagocyte's lysosomal enzymes.

Plasma membranes are thought to remain intact during apoptosis, until the last stages, when they become permeable to normally retained solutes.

On histologic examination, in tissues stained with hematoxylin and eosin, the apoptotic cell appears as a round or oval mass of intensely eosinophilic cytoplasm with fragments of dense nuclear chromatin. Because the cell shrinkage and formation of apoptotic bodies are rapid and the pieces are quickly phagocytosed, considerable apoptosis may occur in tissues before it becomes apparent in histologic sections. In addition, apoptosis—in contrast to necrosis—does not elicit inflammation, making it more difficult to detect histologically.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-53)

■ **Pathogenesis of apoptosis:** Apoptosis is the end-point of an energy-dependant cascade of molecular events, initiated by certain stimuli, and consisting of four separable but overlapping components:

1. **Signaling pathways** that initiate apoptosis.
  - Extrinsic or death receptor-initiated pathway.
  - Intrinsic or mitochondrial pathway.
2. **Control & integration**, in which intracellular positive and negative regulatory molecules inhibit, stimulate, or forestall apoptosis and thus determine the outcome.
3. A **common-execution phase** consisting of the actual death program and accomplished largely by the caspase family of proteases.
4. **Removal of dead cells** by phagocytosis.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-53-55)

#### Mechanism of Apoptosis:

1. Intrinsic (mitochondrial) pathway.
2. Extrinsic (death receptor initiated) pathway.

#### Intrinsic pathway:

##### Cell injury

- Lack of survival signal (GF)
- DNA damage (by radiation, free radicals)
- Protein misfolding (ER stress)

↓

Activation of sensors (BH3-only proteins - Bim, Bid, Bad)

↓

Inhibit the action of anti-apoptotic protein (Bcl-2, Bcl-x)

↓

Activation of Bax/ Bak channel

↓

Create channel and leak proteins from inner mitochondrial membrane to cytoplasm.

↓

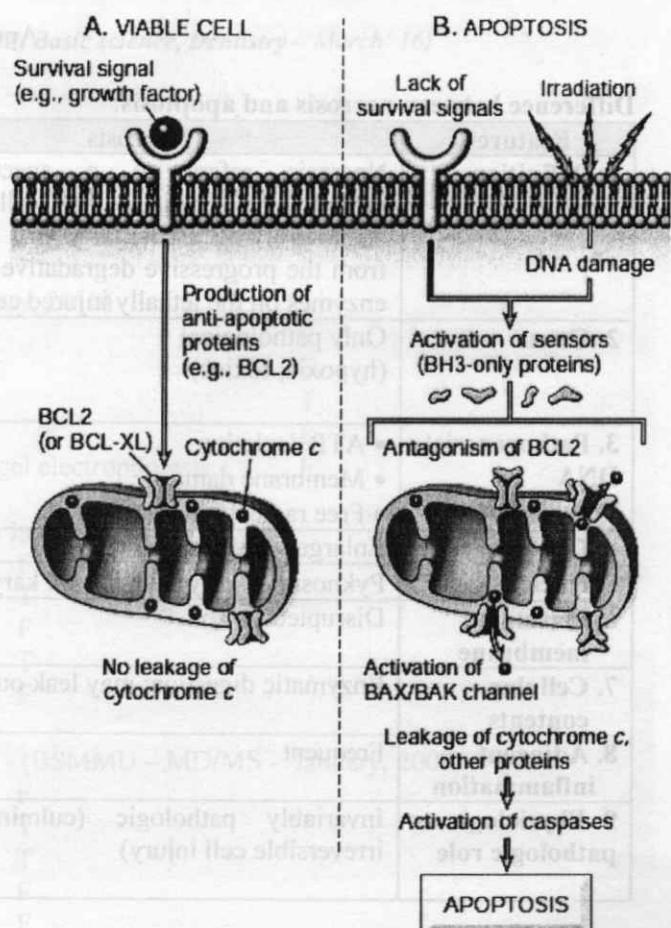
Increase mitochondrial permeability and release proapoptotic molecule (cytchrome c, and other proteins)

↓

Initiation of caspase cascade

↓

Apoptosis.



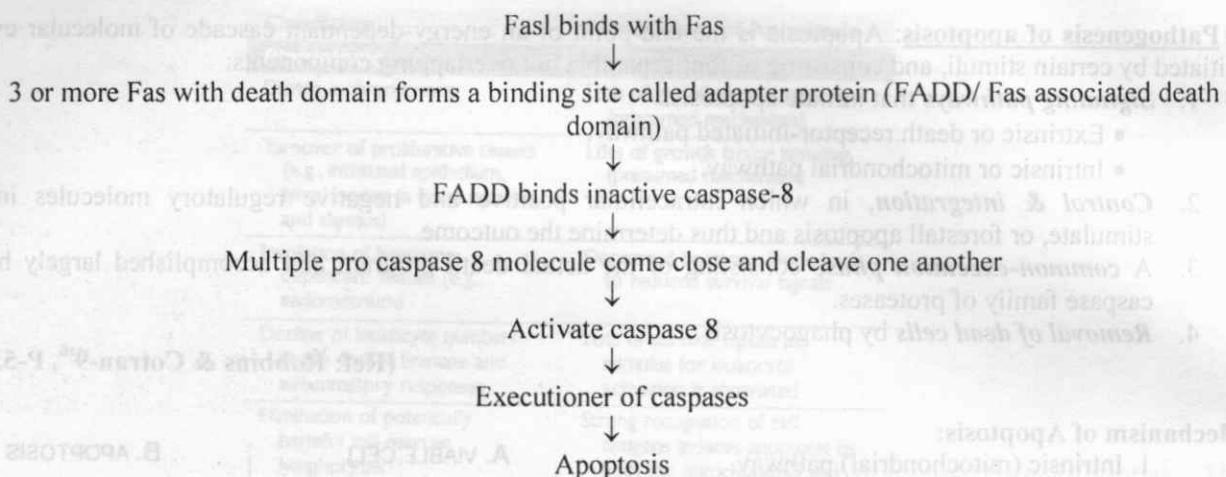
**Fig:** The intrinsic (mitochondrial) pathway of apoptosis. **A**, Cell viability is maintained by the induction of anti-apoptotic proteins such as BCL2 by survival signals. These proteins maintain the integrity of mitochondrial membranes and prevent leakage of mitochondrial proteins. **B**, Loss of survival signals, DNA damage, and other insults activate sensors that antagonize the anti-apoptotic proteins and activate the pro-apoptotic proteins BAX and BAK, which form channels in the mitochondrial membrane. The subsequent leakage of cytochrome c (and other proteins, not shown) leads to caspase activation and apoptosis.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-53-55)

#### Extrinsic pathway:

Death receptor are the member of TNF family and contains a cytoplasmic domain involved in protein-protein interaction which is essential for apoptotic signals.

e.g. Type I TNF receptor (Fas/cd 95), the ligand for Fas is FasL, expressed in cytotoxic T cells.



(Ref: Robbins & Cotran-9<sup>th</sup>, P-56)

#### Difference between necrosis and apoptosis:

Features	Necrosis	Apoptosis
<b>1. Definition</b>	Necrosis refers to a spectrum of morphologic changes that follows cell death in living tissue, largely resulting from the progressive degradative action of enzymes on the lethally injured cell.	<i>Apoptosis</i> is a pathway of cell death that is induced by a tightly regulated suicide program in which cells destined to die activate enzymes that degrade the cells' own nuclear DNA and nuclear and cytoplasmic proteins.
<b>2. Cause</b>	Only pathological (hypoxia, toxins)	<ul style="list-style-type: none"> <li>Physiological (withdrawal of trophic factors or hormones) &amp;</li> <li>Pathological (radiation, drugs, toxins etc)</li> </ul>
<b>3. Pathogenesis/ DNA breakdown</b>	<ul style="list-style-type: none"> <li>ATP depletion</li> <li>Membrane damage</li> <li>Free radical injury</li> </ul>	<ul style="list-style-type: none"> <li>Activation of endonuclease</li> <li>Gene activation</li> <li>Internucleosomal</li> </ul>
<b>4. Cell size</b>	Enlarged (swelling)	Reduced (shrinkage)
<b>5. Nucleus</b>	Pyknosis → karyorrhexis → karyolysis	Fragmentation into nucleosome-size fragments
<b>6. Plasma membrane</b>	Disrupted	Intact; altered structure, especially orientation of lipids
<b>7. Cellular contents</b>	Enzymatic digestion; may leak out of cell	Intact; may be released in apoptotic bodies
<b>8. Adjacent inflammation</b>	Frequent	No
<b>9. Physiologic or pathologic role</b>	Invariably pathologic (culmination of irreversible cell injury)	Often physiologic, means of eliminating unwanted cells; may be pathologic after some forms of cell injury, especially DNA damage.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-40)

Question bank

**Q. Features of apoptosis are (BSMMU – Non-Residency – MD, MS, Basic science – July' 18)**

- a) reduced cell size
- b) disrupted plasma membrane of cells
- c) inflammation in adjacent tissue
- d) fragmentation of cell nucleus
- e) enzymatic digestion of cellular contents

Ans. a) T b) F c) F d) T e) F

**Q. Apoptosis (BSMMU – Residency – Dentistry – March' 18)**

- a) is the normal physiological process of programmed cell death
- b) occurs only in old age
- c) result in products that are removed by phagocytosis
- d) causes the plasma membrane to undergo Meiosis
- e) causes inflammation which may damage surrounding cells

Ans. a) T b) F c) T d) F e) F

**Q. Apoptosis is triggered by (BSMMU – Non-Residency – MD, MS, Basic Science & Dentistry – July' 17)**

- a) p53
- b) BCL<sub>2</sub>
- c) ligation of Fas
- d) superoxide dismutase
- e) nitric oxide

Ans. a) T b) F c) T d) F e) F

**Q. Regarding apoptosis (BSMMU – Residency – MD, MS, Basic science, Dentistry – March' 16)**

- a) it is a programmed cell death
- b) the death cells are rapidly cleared
- c) inflammation surrounds the apoptotic focus
- d) cell membrane damage is a constant feature
- e) it may co-exist with necrosis

Ans. a) T b) T c) F d) F e) T [Necroptosis]

**Q. Features of apoptosis are: (BSMMU – MD – January, 2010)**

- |   |   |
|---|---|
| a) cellular swelling  | F |
| b) karyolysis   | F |
| c) intact plasma membrane   | T |
| d) accumulation of neutrophils                                    | F |
| e) ladder pattern of DNA fragments in agarose gel electrophoresis | F |

**Q. Features of apoptosis include - (DMC – MD/ MS - January, 2010)**

- |                                |   |
|--------------------------------|---|
| a. cellular swelling           | F |
| b. fragmentation of nucleus    | T |
| c. plasma membrane damage.     | F |
| d. formation of apoptotic body | T |
| e. Endo-mitosis                | F |

**Q. Morphological features in apoptotic cells include - (BSMMU – MD/MS - January, 2009)**

- |                           |   |
|---------------------------|---|
| a) nuclear fragmentation  | F |
| b) chromatin condensation | T |
| c) cytoplasmic blebs      | T |
| d) cell swelling          | F |
| e) nuclear pyknosis       | F |

**Q. Morphological appearance of apoptosis- (BSMMU-MD/MS-07Ja)**

- a. Shrinkage of cell size T
- b. Inflammatory response around it F
- c. Involvement of large number of cells F
- d. Formation of cytoplasmic membrane blebs T
- e. Densely basophilic cytoplasm F

**Q. Structural changes seen in apoptosis include - (BSMMU - M. Phil, Diploma, July-05)**

- A. chromatin clumping F
- B. chromatin condensation and fragmentation T
- C. cytoplasmic blebs T
- D. organellar swelling F
- E. formation of apoptotic bodies T

**Q. The following diseases are due to increased apoptosis: (MD/MS (DMC)-05Ja)**

- a) Auto immune disorders F
- b) Spinal muscular atrophy T
- c) AIDS. T
- d) Myocardial infarction T
- e) Viral hepatitis. T

**Q. Apoptosis is responsible for- (BSMMU – MD/MS - 05Ja)**

- A. pathologic atrophy of pancreas after duct obstruction T
- B. muscle atrophy in poliomyelitis F
- C. cell death in certain viral hepatitis T
- D. pathological atrophy of hormone dependent tissue F
- E. cell death in chronic osteomyelitis F

**Q. Morphologically apoptosis is characterized by- (MD/MS (DMC)-03Ja)**

- a) Cell shrinkage T
- b) Chromatin condensation T
- c) Cytoplasmic bleb formation T
- d) Phagocytosis of apoptotic bodies by adjacent healthy cells F (macrophage)
- e) Involvement of large group of cells F

**Necroptosis and Pyroptosis****Q. Necroptosis is seen in (BSMMU –Residency – MD, MS, Basic Science – March '18)**

- a) acute pancreatitis
- b) tuberculosis
- c) reperfusion injury
- d) atrophy of seminiferous tubules
- e) Parkinson disease

**Ans.** a) T b) F c)T d) F e)T

**Q. Necroptosis (BSMMU – Residency - MD, MS, Basic Science, Dentistry - March '17)**

- a) is genetically programmed
- b) is characterized by loss of ATP
- c) involves caspase activation pathway
- d) shows rupture of cell membrane
- e) is exclusively pathological

**Ans.** a) T b)T c) F d) T e) F

**Help link:**

- Necroptosis resembles necrosis morphologically and apoptosis mechanistically as a form of programmed cell death.
- Necroptosis is triggered by ligation of TNFR1, and viral proteins of RNA and DNA viruses.
- Necroptosis is caspase-independent but dependent on signaling by the RIP1 and RIP3 complex.
- RIP1-RIP3 signaling reduces mitochondrial ATP generation, causes production of ROS, and permeabilizes lysosomal membranes, thereby causing cellular swelling and membrane damage as occurs in necrosis.
- Release of cellular contents evokes an inflammatory reaction as in necrosis.
- Pyroptosis occurs in cells infected by microbes. It involves activation of caspase-1 which cleaves the precursor form of IL-1 to generate biologically active IL-1. Caspase-1 along with closely related caspase-11 also cause death of the infected cell.

(Ref: Robbins & Cotrans-9<sup>th</sup>, P-59)

### Necroptosis:

- Morphologically necrosis (loss of ATP, swelling of cells, formation of ROS, release of lysosomal enzymes, rupture of plasma membrane, mitochondrial damage)
- Mechanistically apoptosis (programmed cell death)
- Occurs both physiologically and pathologically
- Induced by viral infection
- Triggered by ligation of TNFR1
- Caspase independent,
- RIP & RIP3 dependent
- Occurs in: formation of mammalian bone growth plate, steatohepatitis, acute pancreatitis, reperfusion injury, neurodegenerative disease (parkinson),
- Causes host defence against CMV by inhibiting caspase

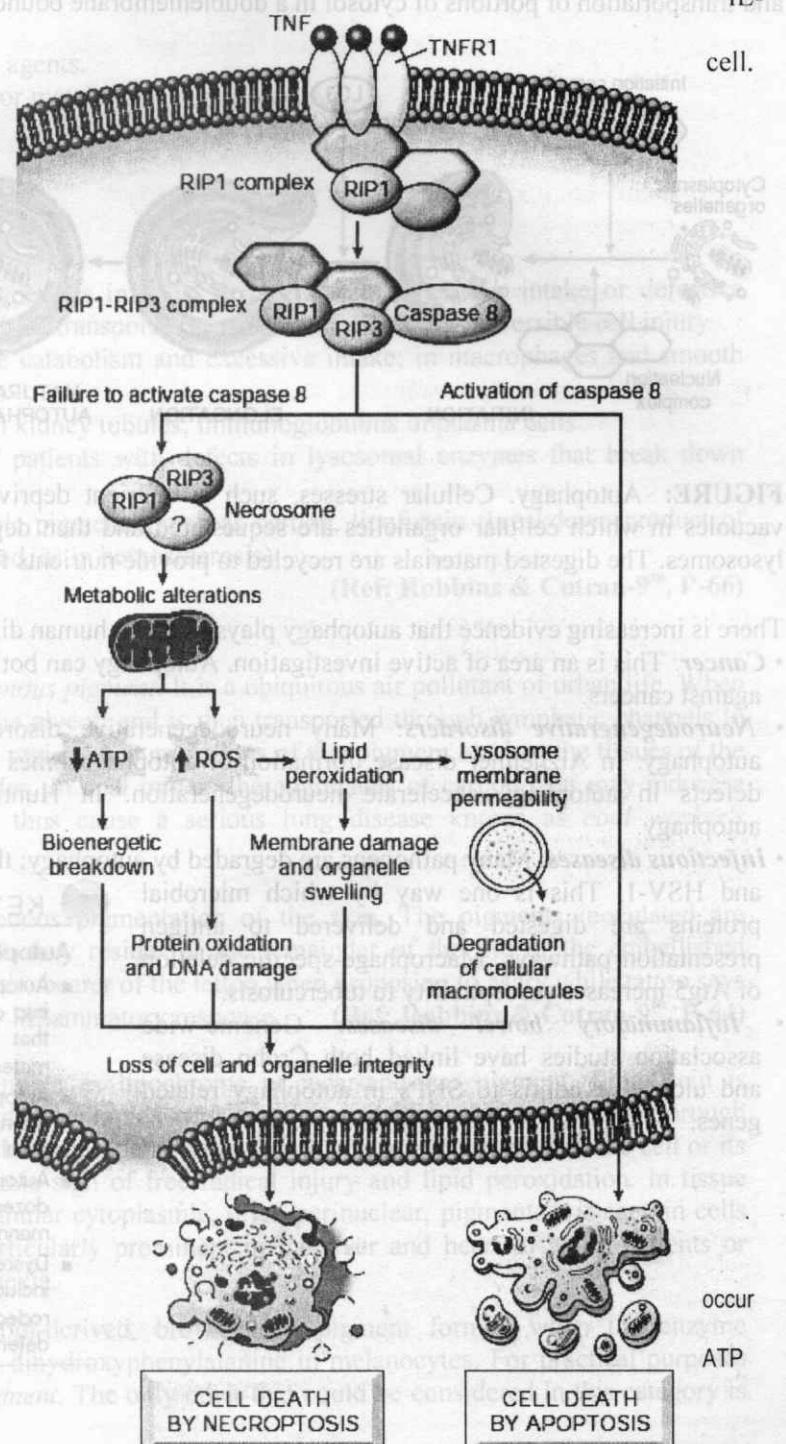


Figure: Molecular mechanism of TNF-mediated necroptosis. Crosslinking of TNFR1 by TNF causes recruitment of RIP1 and RIP3 along with caspase 8. Activation of the caspase leads to apoptosis as described in the text. Inhibition of caspase 8, as may occur in some viral infections, allows RIP1 and RIP3 to initiate signals that affect mitochondrial generation of ATP and ROS. This is followed by events typical of necrosis.

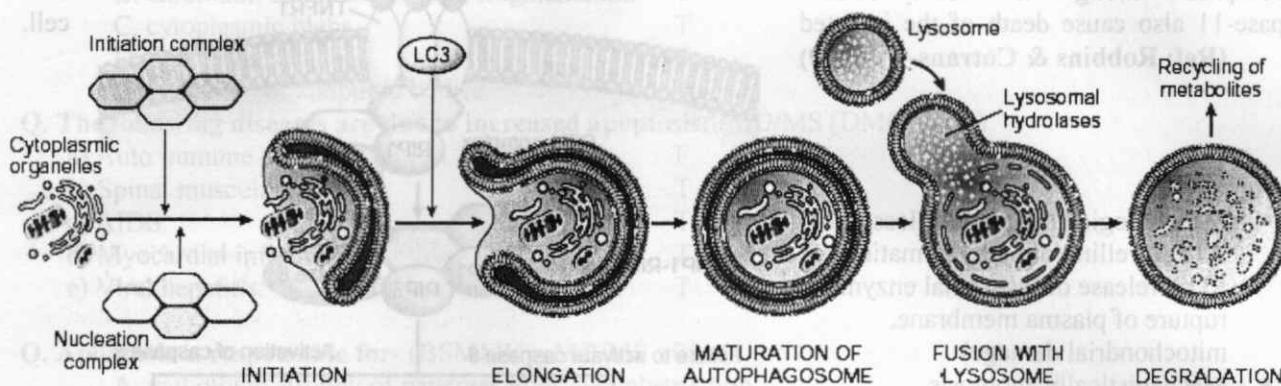
(Ref: Robbins & Cotrans-9<sup>th</sup>, P-59)

## Autophagy

Autophagy is a process in which a cell eats its own contents (*Greek: auto, self; phagy, eating*). It involves the delivery of cytoplasmic materials to the lysosome for degradation.

Depending on how the material is delivered, autophagy can be categorized into three types:

- **Chaperone-mediated autophagy** (direct translocation across the lysosomal membrane by chaperone proteins)
- **Microautophagy** (inward invagination of lysosomal membrane for delivery)
- **Macroautophagy** (hereafter referred to as *autophagy*), the major form of autophagy involving the sequestration and transportation of portions of cytosol in a doublemembrane bound autophagic vacuole (autophagosome)



**FIGURE:** Autophagy. Cellular stresses, such as nutrient deprivation, activate autophagy genes that create vacuoles in which cellular organelles are sequestered and then degraded following fusion of the vesicles with lysosomes. The digested materials are recycled to provide nutrients for the cell. (Ref: Robbins & Cotran-9<sup>th</sup>, P-60)

There is increasing evidence that autophagy plays a role in human diseases. Some examples are listed:

- **Cancer:** This is an area of active investigation. Autophagy can both promote cancer growth and act as a defense against cancers.
- **Neurodegenerative disorders:** Many neurodegenerative disorders are associated with dysregulation of autophagy. In Alzheimer disease, formation of autophagosomes is accelerated and in mouse models genetic defects in autophagy accelerate neurodegeneration. In Huntington disease, mutant huntingtin impairs autophagy.
- **Infectious diseases:** Many pathogens are degraded by autophagy; these include mycobacteria, *Shigella* spp., and HSV-1. This is one way by which microbial proteins are digested and delivered to antigen presentation pathways. Macrophage-specific deletion of Atg5 increases susceptibility to tuberculosis.
- **Inflammatory bowel diseases:** Genome-wide association studies have linked both Crohn disease and ulcerative colitis to SNPs in autophagy related genes.

### KEY CONCEPTS

#### Autophagy

- Autophagy involves sequestration of cellular organelles into cytoplasmic autophagic vacuoles (autophagosomes) that fuse with lysosomes and digest the enclosed material.
- Autophagy is an adaptive response that is enhanced during nutrient deprivation, allowing the cell to cannibalize itself to survive.
- Autophagosome formation is regulated by more than a dozen proteins that act in a coordinated and sequential manner.
- Dysregulation of autophagy occurs in many disease states including cancers, inflammatory bowel diseases, and neurodegenerative disorders. Autophagy plays a role in host defense against certain microbes.

## INTRACELLULAR DEPOSITIONS

### **Intracellular accumulations:**

One of the manifestations of metabolic derangements in cells is the intracellular accumulation of abnormal amounts of various substances.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-61)

### **■ Intracellular accumulations:**

1. **Normal cellular constituents:** water, lipid, protein & carbohydrates.

2. **Abnormal substances:**

- i. Exogenous- mineral or products of infectious agents.
- ii. Endogenous- product of abnormal synthesis or metabolism.

3. **Pigment:** (Normal pigment-melanin)

- i. Exogenous- carbon or coal dust
- ii. Endogenous- lipofuscin, melanin, hemosiderin.

### **■ Deposition of lipids:**

1. **Fatty change:** Accumulation of free triglycerides in cells, resulting from excessive intake or defective transport (often because of defects in synthesis of transport proteins); manifestation of reversible cell injury

2. **Cholesterol deposition:** Result of defective catabolism and excessive intake; in macrophages and smooth muscle cells of vessel walls in atherosclerosis

### **■ Deposition of proteins:** Reabsorbed proteins in kidney tubules; immunoglobulins in plasma cells

### **■ Deposition of glycogen:** In macrophages of patients with defects in lysosomal enzymes that break down glycogen (glycogen storage diseases)

### **■ Deposition of pigments:** Typically indigestible pigments, such as carbon, lipofuscin (breakdown product of lipid peroxidation), or iron (usually due to overload, as in hemosiderosis)

(Ref: Robbins & Cotran-9<sup>th</sup>, P-66)

### **Exogenous Pigments:**

1. **Carbon (coal dust):** The most common *exogenous pigment*. It is a ubiquitous air pollutant of urban life. When inhaled it is picked up by macrophages within the alveoli and is then transported through lymphatic channels to the regional lymph nodes in the tracheobronchial region. Accumulations of this pigment blacken the tissues of the lungs (*anthracosis*) and the involved lymph nodes. In coal miners the aggregates of carbon dust may induce a fibroblastic reaction or even emphysema and thus cause a serious lung disease known as *coal worker's pneumoconiosis*.

2. **Tattooing:** It is a form of localized, exogenous pigmentation of the skin. The pigments inoculated are phagocytosed by dermal macrophages, in which they reside for the remainder of the life of the embellished (sometimes with embarrassing consequences for the bearer of the tattoo when proposing to Mary while tattoo says Valerie!). The pigments do not usually evoke any inflammatory response.      (Ref: Robbins & Cotran-9<sup>th</sup>, P-64)

### **Endogenous Pigments:**

1. **Lipofuscin** is an insoluble pigment, also known as lipochrome or wear-and-tear pigment. Lipofuscin is composed of polymers of lipids and phospholipids in complex with protein, suggesting that it is derived through lipid peroxidation of polyunsaturated lipids of subcellular membranes. Lipofuscin is not injurious to the cell or its functions. Its importance lies in its being a telltale sign of free radical injury and lipid peroxidation. In tissue sections it appears as a yellow-brown, finely granular cytoplasmic, often perinuclear, pigment. It is seen in cells undergoing slow, regressive changes and is particularly prominent in the liver and heart of aging patients or patients with severe malnutrition and cancer cachexia.

2. **Melanin** is an endogenous, non-hemoglobin-derived, brown-black pigment formed when the enzyme tyrosinase catalyzes the oxidation of tyrosine to dihydroxyphenylalanine in melanocytes. For practical purposes melanin is the *only endogenous brown-black pigment*. The only other that could be considered in this category is

homogentisic acid, a black pigment that occurs in patients with *alkaptonuria*, a rare metabolic disease. Here the pigment is deposited in the skin, connective tissue, and cartilage, and the pigmentation is known as *ochronosis*.

3. **Hemosiderin** is a hemoglobin-derived, golden yellow-to-brown, granular or crystalline pigment that serves as one of the major storage forms of iron. Iron is normally carried by specific transport proteins, transferrins. In cells, it is stored in association with a protein, apoferitin, to form ferritin micelles. Ferritin is a constituent of most cell types. Hemosiderin pigment represents aggregates of ferritin micelles. Under normal conditions small amounts of hemosiderin can be seen in the mononuclear phagocytes of the bone marrow, spleen, and liver, which are actively engaged in red cell breakdown.

4. **Bilirubin** is the normal major pigment found in bile. It is derived from hemoglobin but contains no iron. Its normal formation and excretion are vital to health, and jaundice is a common clinical disorder caused by excesses of this pigment within cells and tissues.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-64 + 8<sup>th</sup>, P-38)

**Mechanisms of intracellular accumulations:** There are four main pathways of abnormal intracellular Accumulations.

- Inadequate removal of a normal substance secondary to defects in mechanisms of packaging and transport, as in fatty change (steatosis) in the liver.
- Accumulation of an abnormal endogenous substance as a result of genetic or acquired defects in its folding, packaging, transport, or secretion, as with certain mutated forms of  $\alpha_1$ -antitrypsin.
- Failure to degrade a metabolite due to inherited enzyme deficiencies. The resulting disorders are called *storage diseases*.
- Deposition and accumulation of an abnormal exogenous substance when the cell has neither the enzymatic machinery to degrade the substance nor the ability to transport it to other sites. Accumulation of carbon or silica particles is an example of this type of alteration.

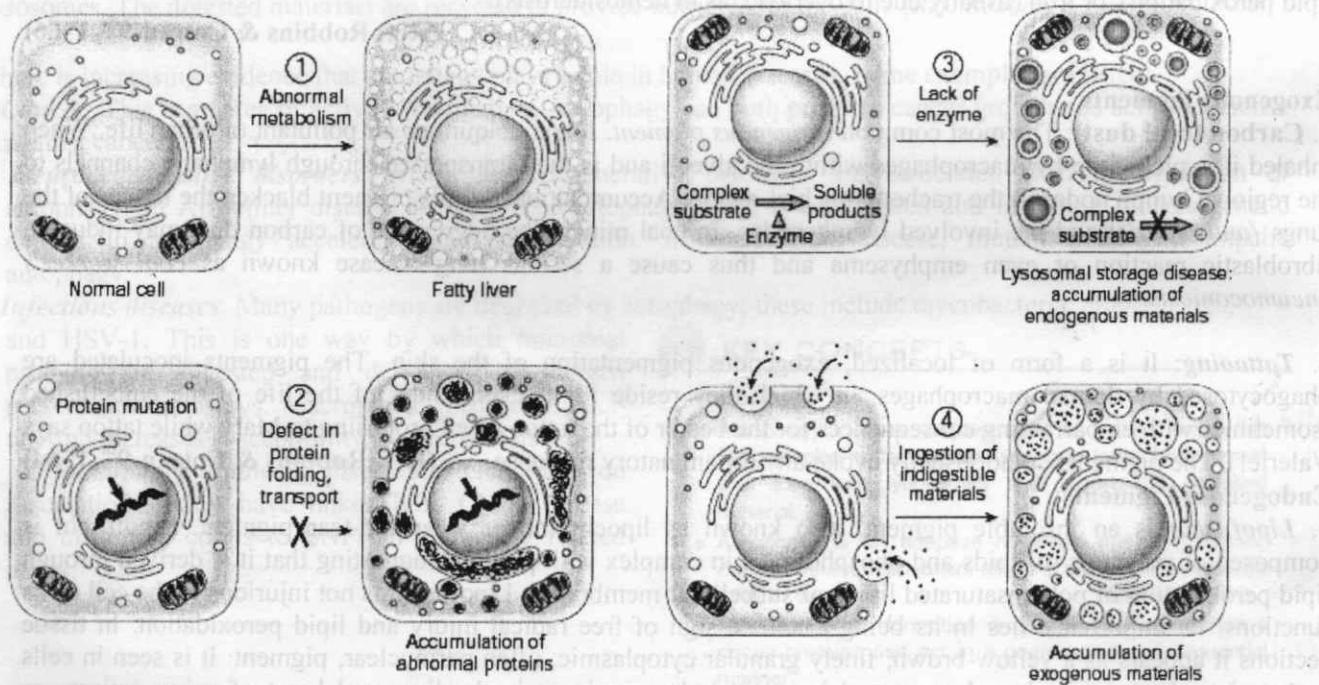


Fig: Mechanisms of intracellular accumulations

(Ref: Robbins & Cotran-9<sup>th</sup>, P-62)

**Question bank**

**Q. Abnormal intracellular depositions are responsible for the following conditions: (BSMMU – MS - January, 2010)**

- |                      |   |
|----------------------|---|
| a) fatty change      | T |
| b) hemosiderosis     | T |
| c) melanoma          | F |
| d) atherosclerosis   | T |
| e) biliary cirrhosis | F |

**Q. The following are endogenous pigments that can be accumulated in the tissue: (BSMMU – MD/MS - January, 2008)**

- |                |   |
|----------------|---|
| a) melanin     | T |
| b) calcium     | F |
| c) hemosiderin | T |
| d) lipofuscin  | T |
| e) amyloid     | F |

**HELP LINK:** see before +

■ **Lipofuscin:** Yellow-brown intra-cytoplasmic granules found in ‘brown atrophy’ of heart

■ **Melanin:**

- It is a brown-black pigment formed in melanocytes.
- Melanophores are macrophages which have engulfed melanin.
- Melanocytes are DOPA positive.
- Tumours: benign naevus and malignant melanoma arise from melanocytes.

■ **Haemosiderin:** Golden yellow to brown pigment giving positive prussian blue reaction. e.g. heart failure cells in chronic passive congestion of lungs.

■ **Bilirubin:** Pigment is visible in severe jaundice

■ **Haematin:** It is a ferric iron and found within macrophages in chronic malaria.

## Cholesterol accumulation

**Q. Accumulation of cholesterol occurs in: (BSMMU – Residency – MD, MS, Basic science, Dentistry – March' 16)**

- |                         |   |
|-------------------------|---|
| a) atherosclerosis      | T |
| b) xanthoma             | T |
| c) anthracosis          | F |
| d) asbestosis           | F |
| e) Niemann-Pick disease | T |

**Help link:**

- Atherosclerosis– intimal layer of aorta & large arteries
- Xanthomas- found in skin & tendon
- Cholesterolemia– found in lamina propria of gall bladder
- Niemann-Pick disease– lysosomal storage disease.  
(Cholesterol accumulation in multiple organs)

**Q. Intracellular accumulation of cholesterol occurs in - (BSMMU – MD/MS - January, 2009)**

- |                                 |   |
|---------------------------------|---|
| a) Alkaptonuria                 | F |
| b) Ochronosis                   | F |
| c) Inflammation                 | T |
| d) Atherosclerosis              | T |
| e) Niemann-Pick disease, type C | T |

**HELP LINK:**

**■ Intracellular accumulation of lipids:**

1. Fatty change (steatosis) refers to abnormal accumulations of triglycerides within the parenchymal cells. e.g.- Liver, heart, muscle and kidney.
2. Cholesterol and cholesterol esters-intracellular accumulation is manifested histologically by intracellular vacuoles are seen in several pathologic processes.
  - a) **Atherosclerosis:** In atherosclerotic plaques smooth muscle cells and macrophages within the intimal layer of the aorta and large arteries are filled with lipid vacuoles. Most of which are made up of cholesterol and cholesterol esters.
  - b) **Xanthomas:** Clusters of foamy macrophages are found in the subepithelial connective tissues of skin and in tendons producing tumorous masses known as xanthomas.
  - c) **Cholesterolemia:** Refers to the focal accumulation of cholesterol-laden macrophages in the lamina propria of the gall bladder.
  - d) **Niemann-Pick disease, type C:** This lysosomal storage disease is caused by mutations affecting an enzyme involved in cholesterol trafficking, resulting in cholesterol accumulation in multiple organs.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-62)**Q. Intracellular accumulations of cholesterol are seen in: (BSMMU - M. Phil, Diploma, July'08)**

- |                                   |   |
|-----------------------------------|---|
| a) atherosclerosis                | T |
| b) xanthoma                       | T |
| c) Niemann - Pick disease, type C | T |
| d) arteriosclerosis               | F |
| e) oncocytoma                     | F |

**Fatty liver****Q. Fatty change of the liver occurs in (BSMMU-Residency - MD/MS, Basic science – March' 14)**

- |                                      |   |
|--------------------------------------|---|
| a) starvation                        | T |
| b) protein energy malnutrition (PEM) | T |
| c) haemochromatosis                  | F |
| d) Wilson's disease                  | F |
| e) obesity                           | T |

**Help link:**

**■ Steatosis (fatty change):** The terms *steatosis* and *fatty change* describe abnormal accumulations of triglycerides within parenchymal cells.

**■ Site:** Fatty change occurs in liver (most common, because it is the major organ involved in fat metabolism), heart, muscle & kidney.

**Type of fatty liver:**

1. **Acute fatty liver:** Acute fatty liver is a rare but serious condition associated with acute liver failure. In acute fatty liver triglycerides accumulates as small, -membrane-bound droplets in the cytoplasm (microvacular fatty change).
2. **Chronic fatty liver:** Is much more common. It is associated with chronic alcoholism, malnutritions and several hepatotoxins. Fat droplets in the cytoplasm fuse to form progressively larger globules (macrovacular fatty change).

**■ Causes of steatosis:**

- Toxins: e.g. CCl<sub>4</sub>
- Protein malnutrition
- Diabetes mellitus
- Obesity
- Starvation
- Anoxia

- In developed nations the most common causes of significant fatty change in the liver (fatty liver) are alcohol abuse.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-62)

### Causes of steatosis:

#### Macrovascular steatosis:

- Alcohol
- Obesity
- Diabetes mellitus
- Rapid weight reduction
- Starvation
- Malabsorption
- Parenteral nutrition
- Intestinal bypass operation
- Drugs: iron, amiodarone

#### Microvascular steatosis:

- Fatty liver of pregnancy
- Reye's syndrome
- Drugs: Na valproate, ketoprofen, didanosine
- Inherited metabolic disorders: urea cycle defects, fatty acid oxidation defects, lysosomal acid esterase deficiency

**Mechanism of TG accumulation in the liver:** Excess accumulation of triglycerides within the liver may result from excessive entry or defective metabolism and export of lipids. The mechanisms are the followings:

- Excess entry of free fatty acid from adipose tissue or ingested food into hepatocytes e.g. in Starvation, and DM.
- Increased fatty acid synthesis from acetate.
- Decreased oxidation of fatty acid (into ketone bodies & CO<sub>2</sub>) due to anoxia.
- Increased esterification of fatty acid to triglycerides due to increased supply of α-glycerophosphate e.g. in alcoholism.
- Decreased synthesis of apoproteins due to protein energy malnutrition and CCl<sub>4</sub> poisoning.
- Impaired lipoprotein secretion from the liver.

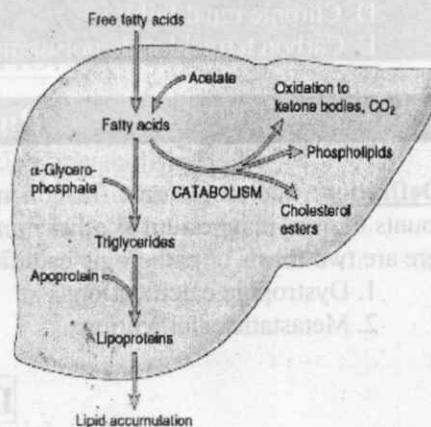


Fig: Mechanism of accumulation of TG in fatty liver  
(Ref: Robbins & Cotran-8<sup>th</sup>, P-34)

**Q. Fatty liver: (BSMMU – Residency – MD – March '13)**

- Is common in diabetic patient
- Is always fatal
- Is associated with metabolic syndrome
- Can give rise to cirrhosis of liver
- Is treated by sitagliptan

**Ans:** a) T b) F c) T d) T e) F

**Q. Non-alcoholic fatty liver disease: (BSMMU – MD – January, 2010)**

- is seen mostly in nutritional deficiency states T
- invariably progress to cirrhosis F
- is more common in diabetics T
- do not show Mallory's hyaline in liver biopsy F
- is initiated with increased fatty acid influx T

#### HELP LINK:

'The mallory body' or 'alcoholic hyaline' is an eosinophilic intracytoplasmic inclusion in the liver cells that is characteristic of alcoholic liver disease although, it can be present in other conditions.

**Q. Steatosis – (BSMMU – MD/MS - January, 2009)**

- |   |   |                             |
|---|---|-----------------------------|
| a) is caused by alcohol abuse only      | F | [False – because of ‘only’] |
| b) may lead to cirrhosis                | T |                             |
| c) may lead to hepatocellular carcinoma | T |                             |
| d) is only seen in liver                | F | [False – because of ‘only’] |
| e) may occur in heart                   | T |                             |

**Q. Mechanisms of fatty change of the liver are: (BSMMU - M. Phil, Diploma, July-'09)**

- |  |   |  |
|--|---|--|
| a) Increased free fatty acid delivery to liver | T |  |
| b) Liver cell apoptosis                        | F |  |
| c) Reversible liver cell injury                | T |  |
| d) Increased formation of triglyceride         | T |  |
| e) Decreased formation of apoprotein           | T |  |

**Q. The following conditions usually lead to fatty liver - (BSMMU - M. Phil, Diploma, July-04)**

- |                                   |   |  |
|-----------------------------------|---|--|
| A. Fatty food intake              | T |  |
| B. Chronic alcoholism             | T |  |
| C. Protein energy malnutrition    | T |  |
| D. Chronic renal failure          | F |  |
| E. Carbon tetrachloride poisoning | T |  |

## Pathological Calcification

■ **Definition:** Pathologic calcification means the abnormal deposition of calcium salts, together with smaller amounts of iron, magnesium & other mineral salts.

There are two forms of pathologic calcification:

1. Dystrophic calcification:
2. Metastatic calcification:

### **Dystrophic calcification**

When the deposition occurs locally in dying tissues (areas of necrosis) it is known as **dystrophic calcification**. It occurs despite normal serum levels of calcium and in the absence of derangements in calcium metabolism.

■ **Site:**

1. In areas of necrosis, whether they are of coagulative, caseous, or liquefactive type, and in foci of enzymatic necrosis of fat.
2. In the atheromas of advanced atherosclerosis.
3. In aging or damaged heart valves, further hampering their function.
4. Tuberculous lymph node.

■ **Pathogenesis:** In the pathogenesis of dystrophic calcification, the final common pathway is the formation of crystalline calcium phosphate mineral in the form of an apatite similar to the hydroxyapatite of bone.

Calcium is concentrated in membrane-bound vesicles in cells by a process that is initiated by membrane damage and has several steps:

- 1) calcium ion binds to the phospholipids present in the vesicle membrane;
- 2) phosphatases associated with the membrane generate phosphate groups, which bind to the calcium;
- 3) the cycle of calcium and phosphate binding is repeated, raising the local concentrations and producing a deposit near the membrane; and
- 4) a structural change occurs in the arrangement of calcium and phosphate groups, generating a microcrystal, which can then propagate and lead to more calcium deposition

**■ Morphology:**

**Gross:** The calcium salts appear macroscopically as fine, white granules or clumps, often felt as gritty deposits. Sometimes a tuberculous lymph node is virtually converted to stone.

**Histologically:**

- Calcium salts have a basophilic, amorphous granular, sometimes clumped appearance.
- They can be intracellular, extracellular, or in both locations.
- In the course of time, **heterotopic** bone may be formed in the focus of calcification.
- On occasion single necrotic cells may constitute seed crystals that become encrusted by the mineral deposits.
- The progressive acquisition of outer layers may create lamellated configurations, called **psammoma bodies** because of their resemblance to grains of sand. Some types of papillary cancers (e.g., thyroid) are apt to develop psammoma bodies.
- In asbestos, calcium and iron salts gather about long slender spicules of asbestos in the lung, creating exotic, beaded dumbbell forms

**■ Clinical significance:** It may cause organ dysfunction. e, g. calcified valvular disease, atherosclerosis.

(Ref: Robbins & Cotran's-9<sup>th</sup>, P-65)

## METASTATIC CALCIFICATION

**Definition:** The deposition of calcium salts in normal tissues is known as **metastatic calcification**. It almost always results from hypercalcemia secondary to some disturbance in calcium metabolism.

(Ref: Robbins & Cotran's-9<sup>th</sup>, P-65)

**■ Cause:****1. Increased secretion of parathyroid hormone:** hyperparathyroidism due to

- Parathyroid tumors, and
- ectopic secretion of PTH-related protein by malignant tumors

**2. Resorption of bone tissue:**

- primary tumors of bone marrow (e.g., multiple myeloma, leukemia)
- diffuse skeletal metastasis (e.g., breast cancer),
- accelerated bone turnover (e.g., Paget disease), or
- immobilization

**3. Vitamin D-related disorders:**

- vitamin D intoxication
- sarcoidosis (in which macrophages activate a vitamin D precursor)
- idiopathic hypercalcemia of infancy (Williams syndrome), characterized by abnormal sensitivity to vitamin D.

**4. Renal failure:** which causes retention of phosphate, leading to secondary hyperparathyroidism.**5. Less common causes:**

- aluminum intoxication – it occurs in patients on chronic renal dialysis
- milk-alkali syndrome – it is due to excessive ingestion of calcium and absorbable antacids such as milk or calcium carbonate.

**Sites:** Metastatic calcification may occur widely throughout the body but principally affects the interstitial tissues of the **gastric mucosa, kidneys, lungs, systemic arteries, and pulmonary veins**.

**Pathogenesis:** Though quite different in location, all of these tissues excrete acid and therefore have an internal alkaline compartment that predisposes them to metastatic calcification.

**Morphology:** In all these sites the calcium salts morphologically resemble those described in dystrophic calcification. Thus, they may occur as noncrystalline amorphous deposits or, at other times, as hydroxyapatite crystals.

**■ Clinical significance:**

Deposition in lungs → respiratory defect.

Deposition in kidney → renal damage

Deposition in blood vessels → vascular obstruction.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-65)

**■ Causes of hypercalcaemia:**

A. causes of metastatic calcification: see above.

B. Others:

- Secondary deposit
- Endocrine disease: Thyrotoxicosis, Addison's disease.
- Drugs: Thiazide diuretics.
- Iatrogenic

(Ref: Khaleque's Pathology)

**Question Bank**

**Q. Metastatic calcification is associated with (BSMMU – Non-Residency – MD, MS, Basic Science & Dentistry – July' 17)**

- a) multiple myeloma
- b) aortic stenosis
- c) hyperparathyroidism
- d) atherosclerosis
- e) healing of tuberculous lesions

Ans. a)T b) F c) T d) F e) F

**Q. Common sites of metastatic calcification are (BSMMU – Residency - MD, MS, Basic Science - March' 17)**

- a) gastric mucosa
- b) kidney
- c) systemic arteries
- d) omental fat
- e) abscess cavity

Ans. a) T b) T c) T d) F e) F

**Q. Conditions that give rise to metastatic calcification are (BSMMU – Residency – MS - March' 17)**

- a) atherosclerosis
- b) sarcoidosis
- c) renal failure
- d) pulmonary tuberculosis
- e) multiple myeloma

Ans. a) F b) T c)T d) F e)T

**Q. Dystrophic calcification occurs in (BSMMU – Residency - Dentistry - March' 17)**

- a) atherosclerosis
- b) tuberculosis
- c) sarcoidosis
- d) thyrotoxicosis
- e) asbestosis

Ans. a) T b) T c) F d) F e) T

**Q. Dystrophic calcification (BSMMU – Residency – MD, MS, Basic science, Dentistry – March' 16)**

- a) occurs in normal tissues
- b) is encountered in areas of necrosis
- c) occurs whenever there is hypercalcaemia
- d) is a telltale sign of previous cell injury
- e) appears microscopically as fine white granules

Ans. a) F b) T c) F d) T e) F

**Q. Metastatic calcification can occur in (BSMMU – Non-Residency – MD, MS, Basic science – July' 15)**

- |                           |   |
|---------------------------|---|
| a) sarcoidosis            | T |
| b) renal failure          | T |
| c) pulmonary tuberculosis | F |
| d) multiple myeloma       | T |
| e) myocardial infarction  | F |

**Q. Dystrophic calcification can occur in (BSMMU – Residency – MD, MS, Basic – March' 15)**

- a) fat necrosis
- b) carcinoma of thyroid
- c) parathyroid adenoma
- d) tuberculous lymphnode
- e) sarcoidosis

Ans. a) T b) T c) F d) T e) F

**Q. Pathological calcification may be seen in the following conditions (BSMMU –Residency - MD/MS, Basic science – March' 14)**

- |                                      |   |
|--------------------------------------|---|
| a) Hodgkin's lymphoma                | F |
| b) oligodendrogloma                  | T |
| c) enzymatic fat necrosis            | T |
| d) in fatty liver                    | F |
| e) in papillary carcinoma of thyroid | T |

**Q. The sites of metastatic calcification are: (BSMMU – Non-Residency - MD/MS, Basic science – 13Ju; M. Phil, Diploma (Non-Residency) – 11Ju, DMC & others – MD – 11Ju)**

- a) the kidney
- b) the wall of the inferior vena cava
- c) old tuberculous lesions
- d) atheroma
- e) the cornea

Ans.

- a) **True.** In pathological conditions associated with hypercalcaemia and hypercalciuria, calcium is deposited in the tubular epithelial cells causing cellular damage. Calcified cellular debris then blocks the tubular lumen causing an obstructive atrophy of the nephrons with interstitial fibrosis. Atrophy of the entire cortical areas drained by the damaged tubules may occur leading to cortical scarring. The earliest functional defect is an inability to elaborate a concentrated urine.

- b) False. Calcification is rare in the walls of veins, possibly because of the high CO<sub>2</sub> content of venous blood and the low pH.
- c) False. The calcification which occurs in old tuberculous lesions is dystrophic calcification. It occurs in tuberculous lesions because of the high fat content of caseous pus. This is due to the high lipid content of the M. tuberculosis which is liberated from the bacillus when it dies.
- d) False. Calcification certainly occurs in atherosomatous plaques but this is also dystrophic in nature. Calcium is deposited because of the high concentration of lipid in atheroma.
- e) True. The cornea is frequently affected and the condition can be discovered during life by slit lamp examination. (Ref: Smiddy)

**Q. Metastatic calcification occurs in following diseases (BSMMU – MD/MS (Residency) – January, 2011)**

- |  |   |
|--|---|
| a) parathyroid hyperplasia                   | T |
| b) breast carcinoma with skeletal metastasis | T |
| c) sarcoidosis                               | T |
| d) papillary carcinoma of thyroid            | F |
| e) prostatic carcinoma                       | F |

**Q. Causes of metastatic calcification are: (BSMMU – MS - January, 2010)**

- |   |   |
|---|---|
| a) increased intake of calcium in young age | F |
| b) parathyroid adenoma                      | T |
| c) leukaemia                                | T |
| d) acute renal failure                      | F |
| e) sarcoidosis                              | T |

**Q. Sites of metastatic calcifications are: (BSMMU - M. Phil, Diploma, July-09)**

- |                           |   |
|---------------------------|---|
| a) Gastric mucosa         | T |
| b) Kidney                 | T |
| c) Aging heart valve      | F |
| d) Tuberculous lymph node | F |
| e) Lung                   | T |

**Q. Causes of dystrophic calcification are - (MD/MS (DMC)-09Ja)**

- |                        |                                     |
|------------------------|-------------------------------------|
| a. multiple myeloma    | F                                   |
| b. Cushing syndrome    | F                                   |
| c. tuberculosis        | T                                   |
| d. abscess             | T [Liquefactive necrosis - abscess] |
| e. hyperparathyroidism | F                                   |

**HELP LINK:**

**■ Example of dystrophic calcification:**

1. Necrotic tissues:
  - Caseous necrosis of tubercle
  - Fat necrosis
  - Liquefaction necrosis
2. Advanced atherosomatous lesions
3. Hematoma
4. Thrombosis
5. Infarcts
6. Heart valve e.g. subacute infective endocarditis
7. Other sites:
  - Uterine fibroids
  - Meningioma
  - Constrictive pericarditis
  - Dead fetus • Dead parasites

**Q. Causes of hypercalcaemia are- (MD/MS (DMC)-08Ja)**

- |                      |   |
|----------------------|---|
| a) Multiple myeloma  | T |
| b) Osteosarcoma      | F |
| c) Sarcoidosis       | T |
| d) Williams syndrome | T |
| e) Hypophosphatemia  | F |

**Q. Causes of hypercalcaemia include: (MD/MS (DMC)-06Ja)**

- |                          |   |
|--------------------------|---|
| a. Chronic renal failure | F |
| b. Addisons disease      | T |
| c. Hypoalbuminaemia      | F |
| d. Thiazide diuretics    | T |
| e. Multiple myeloma      | T |

**Q. Dystrophic calcification (BSMMU - M. Phil, Diploma, July-06)**

- |  |   |
|--|---|
| a) Occur in absence of any derangement of calcium metabolism | T |
| b) Result in the formation of psammoma bodies                | T |
| c) Seen in association with hyperparathyroidism              | F |
| d) Lead to the heterotopic                                   | T |
| e) Seen in milk-alkali syndrome                              | F |

**Q. Dystrophic calcification- (BSMMU – MD/MS - 05Ja)**

- |  |   |
|--|---|
| A. is seen in dead tissues                               | T |
| B. is seen in viable tissues                             | F |
| C. occurs when there is disordered metabolism of calcium | F |
| D. occurs when calcium levels is normal                  | T |
| E. occurs when there is destructive bone lesion          | F |

**Q. Metastatic calcification occur in the following organs: (MD/MS (DMC)-05Ja)**

- |                  |   |
|------------------|---|
| a) Stomach       | T |
| b) lungs         | T |
| c) Cornea        | T |
| d) Blood vessels | T |
| e) Kidney        | T |

**Q. In dystrophic calcification - (MD/MS (DMC)-04Ja)**

- |   |   |
|---|---|
| a) Calcium deposition occurs in dying tissue.     | T |
| b) Serum calcium level is high                    | F |
| c) Calcium metabolism is normal                   | T |
| d) Initiation and propagation phases are involved | T |
| e) Crystalline calcium carbonate is formed        | F |

**Q. Dystrophic calcification is seen usually in- (BIRDEM-04)**

- |                           |   |
|---------------------------|---|
| a) Degenerated tissue     | T |
| b) Caseation necrosis     | T |
| c) Hyperparathyroidism    | F |
| d) Renal failure          | F |
| e) Enzymatic fat necrosis | T |

**Q. Metastatic calcification- (MD/MS (DMC)-03Ja)**

- |   |   |
|---|---|
| a) Is associated with hypercalcemia       | T |
| b) Can occur in renal failure             | T |
| c) Is encountered in areas of necrosis    | F |
| d) Is almost inevitable in atheromas      | F |
| e) Principally affects the gastric mucosa | T |

**Q. Metastatic calcification occurs in – (BSMMU-MD/MS - 02Ja)**

- |   |   |
|---|---|
| a) Increased secretion of parathyroid         | T |
| b) Decreased secretion of parathyroid hormone | F |
| c) Vit-D related disorders                    | T |
| d) Vit-C related disorders                    | F |
| e) Renal failure                              | T |

**Q. Metastatic calcification is associated with- (BSMMU-01Ja)**

- |                                  |   |
|----------------------------------|---|
| a) Hypercalcaemia                | T |
| b) Normal calcium level          | F |
| c) Areas of necrosis             | F |
| d) Increased parathyroid hormone | T |
| e) Vit- D related disorders      | T |

## Hyaline changes

- Alteration within the cells or extracellular spaces
- Homogenous glassy, pink appearance
- Intracellular hyaline: eg. Reabsorption droplets, russells bodies, alcoholic hyaline,
- Extracellular hyaline: eg. Collagenous tissue in old scar, hyalinized blood vessels in DM, HTN.

## Cachexia

- Found in protein energy malnutrition (marasmus), cancer, chronic inflammatory disorders like TB, sarcoidosis, IBD etc.
- Occurs in 50% of cancer patients (GIT, pancreatic and lung cancers commonly)
- Mechanisms: proteolysis inducing factors, lipid mobilizing factors (proinflammatory cytokines, IL-6, TNF/cachectin).
- These causes suppressed appetite and depletion of lipid, wasting of muscle or atrophy.

## Cellular Aging

**Q. Cellular aging (BSMMU – Residency – MD, MS, Basic Science – March' 18)**

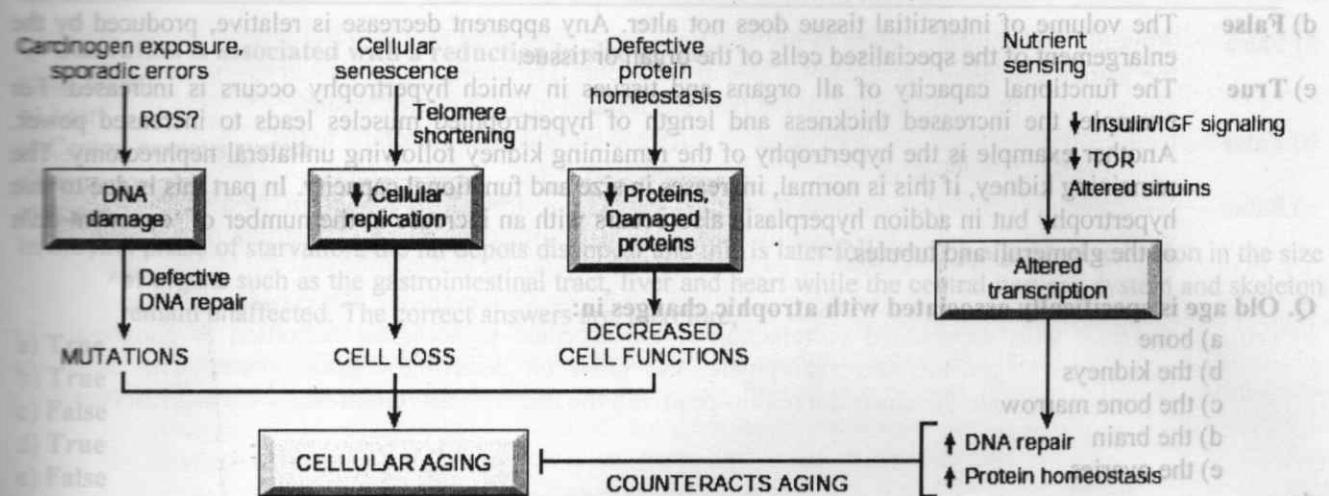
- |  |
|--|
| a) results from DNA damage                           |
| b) is characterized by genetic instability           |
| c) is not modified by total calorie intake           |
| d) results from elongation of telomerase             |
| e) results from activation of tumor suppressor genes |

Ans. a) T b) T c) F d) F e) T

### Help link:

- Cellular aging results from a combination of accumulating cellular damage (e.g., by free radicals), reduced capacity to divide (replicative senescence), reduced ability to repair damaged DNA, and defective protein homeostasis.
- **Accumulation of DNA damage:** Defective DNA repair mechanisms; conversely, caloric restriction activates DNA repair and is known to prolong aging in model organisms
- **Replicative senescence:** Reduced capacity of cells to divide secondary to progressive shortening of chromosomal ends (telomeres)
- **Defective protein homeostasis:** Resulting from impaired chaperone and proteasome functions.
- **Nutrient sensing system:** Caloric restriction increases longevity. Mediators may be reduced IGF-1 signaling and increases in sirtuins.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-68)

(Ref: Robbins-9<sup>th</sup>, P-67)

## IMPORTANT MCQ OF CELL INJURY

[Ref: Smiddy]

**Q. Disuse atrophy follows:**

- a) Blockage of the duct of an exocrine gland
- b) immobilisation of a joint
- c) interference with the nerve supply to the muscles controlling joint movement
- d) interference with the blood supply
- e) the diminished secretion of trophic hormones

Ans.

- a) True** An excellent example is the pancreas. Ligation of the main pancreatic duct leads to atrophy of the exocrine portion of the gland but the endocrine portion, i.e. islets of Langerhans, continue to function normally.

- b) True** Immobilisation of the knee provides a good example. An internal derangement of this joint, such as damage to a cartilage, is rapidly followed by atrophy of the quadriceps group of muscles, especially of vastus medialis.

- c) False** Interruption of the nerve supply to a group of muscles causes a specific neuropathic atrophy in the affected group of muscles. However, the bone to which such muscles are attached may undergo true atrophy due simply to inactivity if the condition is irreversible, e.g. anterior poliomyelitis.

- d) False** Reduction of the blood supply to a tissue causes atrophy due to defective nutrition.

- e) False** The diminished secretion of trophic hormones such as  $T_4$  by the thyroid does produce atrophic changes in target organs such as the skin, hair follicles, sweat gland and sebaceous glands but this is not disuse atrophy. These changes can be readily reversed by the administration of thyroxine.

**Q. Hypertrophy is associated with:**

- a) an increase in the number of visible mitoses
- b) an increase in the bulk of a tissue
- c) an increase in the number of cells in an organ or tissue
- d) an absolute decrease in interstitial tissue
- e) an increase in functional capacity

Ans.

- a) False** In pure hypertrophy the number of cells remains the same in contrast to hyperplasia in which the number of cells increases. No evidence of excessive mitoses is, therefore, normally seen.

- b) True** This is the chief change in hypertrophy. It is seen to best advantage in the hypertrophied muscles of an athlete or in the cardiac muscle in response to hypertension, aortic stenosis or regurgitation.

- c) False** Pure hypertrophy is not associated with an increase in the number of cells but only with an increase in the size of those already present.

- d) False** The volume of interstitial tissue does not alter. Any apparent decrease is relative, produced by the enlargement of the specialised cells of the organ or tissue.
- e) True** The functional capacity of all organs and tissues in which hypertrophy occurs is increased. For example, the increased thickness and length of hypertrophied muscles leads to increased power. Another example is the hypertrophy of the remaining kidney following unilateral nephrectomy. The remaining kidney, if this is normal, increases in size and functional capacity. In part this is due to true hypertrophy but in addition hyperplasia also occurs with an increase in the number of 'concentric cells' of the glomeruli and tubules.

**Q. Old age is specifically associated with atrophic changes in:**

- a) bone
- b) the kidneys
- c) the bone marrow
- d) the brain
- e) the ovaries

**Ans.**

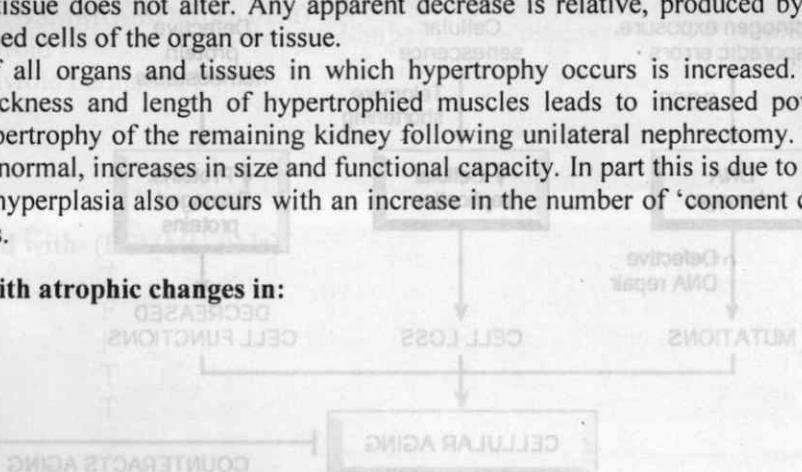
- a) True** The radiological density of bone progressively decreases in both men and women with advancing age. This change is indistinguishable from osteoporosis, in which condition the amount of uncalcified bone may become so great that bone pain and fractures may occur.
- b) True** Increasing age is associated with a gradual loss in the number of nephrons and a gradual reduction in renal functional capacity. At ninety years of age the overall function of kidneys has diminished by about 50%. The decrease of glomerular filtration is particularly important in relation to the administration of drugs such as digitalis and some antibiotics.
- c) True** Gradual replacement of the red marrow takes place with advancing age.
- d) True** Old age is associated with loss of neurons and neuroglial overgrowth causing senile or presenile dementia. These changes occur more rapidly in the presence of ischaemia.
- e) True** Ovarian atrophy is associated with a decline in weight of these organs from approximately 14 g to around 5 g in the sixth decade. The primordial follicles largely disappear and marked stromal hyperplasia occurs.

**Q. Post menopausal ovarian atrophy is associated with the following structural changes:**

- a) stromal hyperplasia
- b) loss of ovarian weight
- c) a proportionate decrease in size of the medulla
- d) disappearance of primordial follicles
- e) persistence of the germinal epithelium

**Ans.**

- a) True** Marked stromal hyperplasia occurs after 40 years of age, possibly due to continued hormone production by the ovaries.
- b) True** The weight of the premenopausal ovary is about 14 g; by the fifth, sixth and seventh decades it falls to 5 g.
- c) False** Relative to the cortex the medullary portion of the ovary, in which the corpora albicantia are situated, is proportionately larger in the post menopausal ovary. In both areas the stromal elements become fibrotic.
- d) True** Rarely a few immature follicles undergoing maturation and atresia may be seen in the corticomedullary junction in the first five years after the menopause.
- e) True** The germinal epithelium persists and follows the various convolutions on the surface but in some places, this intimate connection with the surface may be lost and small cysts may form.



**Q. Starvation is associated with a reduction in size of the:**

- a) fat depots
- b) heart
- c) Central nervous system
- d) liver
- e) bones

In the first phase of starvation, the fat depots disappear and this is later followed by a gradual reduction in the size of organs such as the gastrointestinal tract, liver and heart while the central nervous system and skeleton remain unaffected. The correct answers are, therefore,

- a) True
- b) True
- c) False
- d) True
- e) False

An exception to this general pattern occurs in kwashiorkor. In this condition which affects infants and young children in many parts of Southern and Central Africa and the Far East, the diet is deficient in high grade protein but moderately adequate in total calories due to a high carbohydrate intake. Growth is impaired. The liver is enlarged because of fatty infiltration but depleted of RNA and protein.

**Q. Metaplasia, the transformation of one fully differentiated tissue into another, occurs in: (FCPS - Sur – 09Ja, 08Ju)**

- a) connective tissue elements
- b) the gastrointestinal tract
- c) the central nervous system
- d) the biliary system
- e) the urothelium

Ans.

- a) True      True bone may occasionally develop in an operation scar.
- b) True      Metaplasia occurs in some parts of the gastrointestinal tract under abnormal circumstances. A common site is in the mucus secreting columnar epithelium of the anal canal. When this mucosa prolapses through the anal sphincter, as in third degree haemorrhoids or a true rectal prolapse, the resulting chronic irritation results in a change to squamous epithelium.
- c) False      No metaplastic changes occur in the central nervous system.
- d) True      Metaplasia of the gall bladder epithelium occurs in cholelithiasis. Such change may be eventually followed by the development of a squamous cell carcinoma because of a change from tall columnar to a squamous type of epithelium.
- e) True      Epithelial metaplasia is usually associated with a change to a less specialized or complex type of epithelium. The urothelium is an important exception. In the bladder, the presence of chronic inflammation (excluding tuberculosis) leads to cystitis cystica. The transitional epithelium grows downwards in solid clumps into the submucosa and if these become detached a central space may develop and since these cells may acquire mucus-secreting properties the end result is a glandular mucous membrane. A similar process in the ureters leads to the condition of ureteritis cystitis. Calculi in the urinary tract cause the normal transitional epithelium over a period to become squamous in type, a change which may be followed by the development of a squamous carcinoma.

**Q. Gangrene is necrosis together with:**

- a) desiccation
- b) coagulative necrosis
- c) involvement of a limb
- d) infection of the tissue with Gram-positive organisms
- e) putrefaction

Ans.

the excessive release of melanocyte stimulating hormone by the anterior pituitary due to the decline in

- a) False Although the clinician refers to dry gangrene when infarction followed by desiccation has occurred, the pathologist does not recognise this as gangrene. The change in colour in dry gangrene is due to alterations in the haemoglobin of the red cells trapped in the infarcted tissues.
- b) False Colliqueative necrosis may well occur in gangrene but this is not essential to the pathological definition.
- c) False Gangrene occurs in many places other than a limb, e.g. around the mouth, in the abdominal wall and in the perineum, but is then usually associated with infection, e.g. by Clostridia or microaerophilic streptococci.
- d) False The bacteria responsible for the specific condition of gas gangrene are Gram-positive.
- e) True Necrosis with superadded putrefaction is the accepted pathological definition of gangrene. The responsible organisms are saprophytic, i.e. grow on decaying organic matter. The organisms concerned include the clostridia (Gram-positive), the bacteroides (Gram negative) and fusobacterium (Gram-negative).

**Q. Infarction may occur as a complication in the following diseases:**

- a) atherosclerosis  
 b) Monckeberg's sclerosis  
 c) benign hypertension  
 d) sickle-cell anaemia  
 e) idiopathic thrombocytopenic purpura

Ans.

- a) True Infarction may occur in any organ or tissue supplied by an atherosclerotic artery. It is caused by the sudden obstruction to the blood flow by occlusion of the lumen of the artery. This follows a subintimal haemorrhage in the wall of the diseased artery or thrombosis upon the intimal plaque. Typical infarcts of this nature occur in the heart, brain and limbs.
- b) False This is a condition affecting the major arteries of the lower limb in elderly people caused by dystrophic calcification of the media. The intima is unaffected and the lumen of the artery remains of normal diameter unless coincidental atherosclerotic changes have also occurred in the involved blood vessels.
- c) False Hypertension does not lead to infarction unless accompanied by atherosclerosis. In the brain hypertension may be associated with the development of microaneurysms of the deep penetrating arteries. These tend to rupture causing cerebral haemorrhage.
- d) True Sickle-cell anaemia is frequently complicated by vascular occlusive episodes which lead to infarcts in the lungs, spleen, bone, liver or intestine. In severe cases these episodes occur within the first few years of life but they do not occur in the newborn, however severe the disease, because of the high complement of fetal haemoglobin and low percentage of HbS in the erythrocytes.
- e) False ITP occurs chiefly in children and young adults and is frequently a self-limiting disease which improves within three months. This condition is associated with bleeding from the endometrium, kidneys or gastrointestinal tract if the platelet count is below 2,00,000 per  $\mu\text{ml}$ .

**Q. Liquefaction associated with necrosis occurs after infarction of the:**

- a) heart  
 b) kidney  
 c) brain  
 d) liver  
 e) spleen

F  
 F  
 T  
 F  
 F

In the heart, kidney, liver and spleen coagulative necrosis occurs. The necrotic area becomes swollen, firm, dull and lustreless. Histologically the outlines of the dead cells are usually visible under a light microscope and the dead tissue becomes firm because of the action of tissue thromboplastins on fibrinogen which, together with other plasma proteins, diffuse from the damaged membranes of the necrotic cells.

In contrast brain tissue, which has a large fluid component, becomes 'softened' when necrotic and finally turns into a turbid liquid. The histological architecture of the affected tissue is lost. This is colliqueative necrosis.

**Q. Generalized pigmentation of the skin occurs in:**

- a) carcinoma of the head of the pancreas
- b) idiopathic hereditary haemochromatosis
- c) argyria
- d) arsenic poisoning
- e) black liver disease

**a) True** One of the first clinical manifestations of carcinoma of the head of the pancreas may be the onset of jaundice due to increasing compression of the common bile duct. The colour of the skin tends to be olive green due to the retention of biliverdin. Removal of the obstruction does not result in an abrupt return to normal due to the strong affinity of elastic tissue for bile pigments.

**b) True** Idiopathic hereditary haemochromatosis is one of the commonest inborn errors of metabolism, transmitted as an autosomal recessive, the gene being located in the short arm of Chromosome 6. Excessive dietary iron absorption takes place and is stored as haemosiderin or ferritin. Symptoms develop when about 20 g of stored iron has occurred. The metal is stored in the liver eventually causing micronodular cirrhosis, in the interstitial tissues of the heart causing heart failure and in the pancreas both in the exocrine and islets leading to diabetes, and in the joints. Disruption of the islets results in diabetes hence the alternative name for the condition of 'bronzed diabetes', from the slate grey pigmentation caused by the accumulation of haemosiderin in the dermal macrophages and fibroblasts.

**c) True** The prolonged administration of remedies containing silver preparations is followed by the deposition of brownish granules of silver compounds in the skin, gut wall and basement membrane of the glomeruli and renal collecting tubules.

**d) False** Chronic exposure to arsenic leads to gastrointestinal upset, weakness, weight loss and muscle pains. Individuals who recover from arsenical poisoning commonly develop peripheral neuropathy, desquamation of the skin and hyperpigmentation and hyperkeratosis of the palms and soles of the feet.

**e) False** This is a synergistic infection found in sheep in which *Clostridium pilosporum* is frequently harboured in the liver in the absence of disease. Should the animal become infected with the liver fluke, *Fasciola hepatica*, the local conditions created favour the growth of the clostridia and the animal develops a condition known as black liver disease.

**Q. Patchy skin pigmentation occurs in the following conditions:**

- a) Peutz—Jeghers syndrome
- b) familial polyposis
- c) Addison's disease
- d) purpura
- e) vitiligo

**a) True** The Peutz—Jeghers syndrome is an autosomal dominant disease. The external marker of the condition is patchy circumscribed circumoral and intraoral melanotic pigmentation. The chief importance of the condition, however, is the development of hamartomatous polyps which are chiefly situated in the small bowel causing intermittent attacks of small bowel colic due to the intussusceptions which they provoke. However, in about one third of all patients similar polyps are found in the stomach and large bowel. This type of polyp has no malignant potential but there is an overall increased frequency of carcinoma of the pancreas, breast, ovary and uterus in sufferers of this condition.

**b) False** Pigmentation does not occur in familial polyposis or the related condition known as Gardner's syndrome, in which latter the large bowel polyps are associated with sebaceous cysts, osteomata of the face and skull and desmoid tumours.

**c) False** Addison's disease, due either to a chronic destructive disease of the adrenal by tuberculosis or to an autoimmune phenomenon, is typically associated with a generalized pigmentation of the skin due to the excessive release of melanocyte stimulating hormone by the anterior pituitary due to the decline in

- adrenal inhibition. The hyperpigmentation particularly affects areas of the skin exposed to the sun, pressure points such as the elbows and knees and the knuckles.
- d) **True** Any cause of purpura or bruising leads to temporary localized staining of the skin. This is due to the dermal macrophages retaining some of the iron released from the red cells and incrustation of the collagen molecules with iron.
- e) **False** Vitiligo is a patchy macular form of depigmentation caused by loss of melanocytes; compare this to albinism in which melanocytes are present but melanin is not produced because of a defect in tyrosinase. Vitiligo may be an autoimmune condition, a view supported by the presence of circulating antibodies to melanocytes.

**Q. The normal level of ionised calcium in the plasma is maintained by the following mechanisms:**

- a) the secretion of calcitonin  
 b) the presence of  $1,25(OH)_2D_3$   
 c) parathyroid hormone secretion  
 d) renal tubular conservation  
 e) the circulating level of magnesium

Ans.

- a) **True** Calcitonin is a small polypeptide hormone secreted by specialized 'C' cells which in the mammalian thyroid are derived embryologically from the ultimobranchial organs. The only known physiological regulator of the rate of calcitonin secretion is the concentration of Ca ion in the plasma and extracellular fluid. The chief functions of calcitonin are to regulate calcium homeostasis and bone remodelling. The sensitivity of the human to changing calcium levels is related to age; CT is a much more effective hypocalcaemic agent in the young than the old.
- b) **True**  $1,25(OH)_2D_3$  is the active metabolite of vitamin  $D_3$ . Vitamin  $D_3$  is the natural form of vitamin D in man and is synthesized in the skin from 7-dehydro-cholecalciferol by a photochemical reaction. If because of social factors this process is blocked, the deficiency must be made good by dietary intake. The rate of conversion is determined by the plasma calcium level which exerts its effect indirectly by altering the ratio of secretion of PTH and CT. The major functions of vitamin D are to increase the retention of calcium and  $PO_4$  and secondly to control the mineralisation of bone.
- c) **True** The two chief target organs of PTH are the kidney and bone. An increase in PTH secretion by the parathyroids increases the plasma Ca concentration and decreases the  $PO_4$  concentration and in addition it increases the urinary excretion of phosphate and hydroxyproline-containing peptides.
- d) **True** An increase in the level of circulating PTH decreases the urinary secretion of calcium. Approximately 247000 mmol of calcium are filtered through the glomeruli in a day, but renal conservation is so complete that only 1% is daily excreted in the urine. This is due to the action of PTH on the distal nephron.
- e) **False** Changes in the level of circulating magnesium can occur without the serum calcium level altering. However, hypomagnesaemia may occur in hyperparathyroidism and PTH increases the renal tubular reabsorption of magnesium.

**Q. Hypercalcaemia is associated with:**

- a) increased excitability of the neuromuscular apparatus  
 b) band keratitis  
 c) metastatic calcification  
 d) a prolonged Q-T interval  
 e) renal stones

Ans.

- a) **False** Hypocalcaemia causes increased excitability of the neuromuscular junctions, thus giving rise to the two classical signs known as Trousseau's sign, induced carpopedal spasm on reducing the circulation to the arm by means of a blood pressure cuff and Chvostek's sign, a twitch of the facial muscles following a sharp tap over the facial nerve. Hypercalcaemia is associated with decreased excitability, about twice as much galvanic current being required to excite a peripheral nerve as in the normal

state. This probably accounts for the generalized muscle weakness which can occur in primary hyperparathyroidism.

- b) True** A form of keratitis known as band keratitis occurs in hypercalcaemia from any cause.
- c) True** Metastatic calcification is the deposition of calcium in normal tissues (cf. dystrophic calcification in which calcification takes place in abnormal tissues). Metastatic calcification takes place in any condition in which hypercalcemia occurs, hyperparathyroidism, vitamin D intoxication and the milk-alkali syndrome. The most common sites are the interstitial tissues of blood vessels, kidneys and lungs. The deposits may be amorphous or as hydroxyapatite crystals.
- d) False** The Q-T interval is shortened in any condition in which hypercalcemia develops; a prolonged Q-T interval is a significant finding in hypocalcaemia.
- e) True** Renal stones either composed of calcium oxalate or calcium oxalate phosphate occur in hypercalcemia. Calcium oxalate stones occur in 5% of patients suffering from hypercalcemia, although in about half the patients suffering from this type of calculus hypercalciuria will be present in the absence of hypercalcemia.

**Q. The destruction of bone is associated with the following biochemical changes:**

- a)** an increased secretion of hydroxyproline in the urine
  - b)** an elevated alkaline phosphatase
  - c)** an elevated acid phosphatase
  - d)** an elevated serum calcium
  - e)** depression of the serum phosphate
- Ans.** a) after the attainment of the peak bone mass in young adult life.
- a) True** When bone collagen is destroyed most of it is hydrolysed to its constituent amino acids which are then re-used or degraded further to carbon dioxide and urea. However, 5-8% of collagen is only partially degraded into soluble hydroxyproline-containing peptides which circulate in the blood stream and are excreted in the urine.
  - b) True** Serum alkaline phosphatase comes from three sites: liver, bone and intestine. In normal subjects liver and bone contribute almost equal amounts and the contribution by the intestinal mucosa is small. In conditions causing bone destruction the alkaline phosphatase rises. However, a similar rise also occurs in liver diseases, particularly in biliary cirrhosis. A distinction between liver and bone disease is possible if the concentration of enzymes such as leucine aminopeptidase which is only produced by the cholangioles is determined.
  - c) False** This enzyme is synthesized in the prostate and its level is usually elevated in the presence of a malignant prostate particularly if skeletal secondaries are present. Both the alkaline and acid phosphatases may be raised in this situation because typical prostatic secondary deposits are associated not only with destruction but also the laying down of new bone, producing osteoplastic or sclerotic metastases.
  - d) True** The level of the serum calcium rises in the presence of severe bone destruction, e.g. when generalized osteolytic bone deposits are present leading to hypercalcemia and metastatic calcification particularly in the kidney.
  - e) True** The relationship between calcium and phosphate is reciprocal. Any condition, such as bone destruction, which raises the circulating level of calcium is normally associated with a depression of the phosphate concentration.

**Q. Hypercalcemia and hypercalciuria is caused by:**

- a)** osteolytic secondary deposits in bone
  - b)** hypervitaminosis D, often referred to as vitamin intoxication
  - c)** parathyroid adenoma or carcinomata
  - d)** tumours of adrenal medulla
  - e)** primary carcinoma of the kidney
- True** All osteolytic secondary deposits cause hypercalcemia and hypercalciuria because of the breakdown of bone and the liberation of calcium.

- b) **True** The administration of excessive quantities of vitamin D leads to an increase in calcium absorption from the gut and hence an increase in the blood calcium followed by hypercalciuria. Given in excessive amounts over a prolonged period, irreversible renal damage may occur due to the development of nephrocalcinosis.
- c) **True** Benign or malignant tumours of the parathyroids or simple hyperplasia results in an increase in the concentration of circulating parathyroid hormone. This causes a variety of effects on the cells found in bone including:
- The activation of adenylyl cyclase in the osteoblasts
  - Stimulation of osteoclast division. The net result is increased bone resorption associated with hypercalcaemia and hypercalciuria.
- d) **False** Tumours of the adrenal medulla secrete noradrenaline and adrenaline which have no effect on the skeleton or the serum calcium.
- e) **False** The only hormone secreted by the kidney is erythropoietin which is one of the many factors controlling the production of red cells. This hormone is produced by the action of a heme enzyme-like factor on a plasma substrate. The regulation of the rate at which erythropoietin is produced is determined by the relationship between the oxygen supply to the kidney and the metabolic needs of that organ.

a) **True** Calcitonin is a small polypeptide hormone secreted by specialized cells in the ultimobranchial gland.

- Q. Excessive osteolci tissue is found in:**
- vitamin D deficiency
  - Muslim women
  - patients on anticonvulsant drugs
  - patients on long-term anticoagulant therapy
  - long-standing obstructive jaundice
- Ans.
- a) **True** A deficiency of vitamin D in adults impairs or blocks the normal mineralisation of osteoid laid down in the remodelling of bone; producing osteomalacia. In growing children, there is also inadequate provisional mineralisation of epiphyseal cartilage leading to rickets. This effect is mediated by the defective absorption of calcium from the gut leading to hypocalcaemia.
- b) **True** Muslim women may have a relatively high incidence of osteomalacia in which excessive osteoid occurs in the skeleton because their extensive clothing prevents vitamin D<sub>3</sub> synthesis from 7-dihydrocholesterol by ultra violet light.
- c) **True** Several anticonvulsant drugs, of which phenytoin is an example, given for prolonged periods may lead to the excessive formation of osteoid. This is probably due to the stimulus these drugs give to the production in the liver of isoenzymes which convert vitamin D to inactive metabolites.
- d) **False** A long term anticoagulant therapy has no effect on vitamin D synthesis or bone development.
- e) **True** The absorption of vitamin D requires the presence of bile salts, absorption normally occurring in the lower part of the small intestine. The vitamin is then hydroxylated in the liver and altered in the kidney to its biologically most active form. A vitamin D deficiency is, therefore, theoretically possible in long standing obstructive jaundice.

**Q. The sites in which metastatic calcification occurs are:**

- the kidney
- the wall of the inferior vena cava
- old tuberculous lesions
- atheroma
- the cornea

Ans.

- a) **True.** In pathological conditions associated with hypercalcaemia and hypercalciuria, calcium is deposited in the tubular epithelial cells causing cellular damage. Calcified cellular debris then blocks the tubular lumen causing an obstructive atrophy of the nephrons with interstitial fibrosis. Atrophy of the entire cortical areas drained by the damaged tubules may occur leading to cortical scarring. The earliest functional defect is an inability to elaborate a concentrated urine.

- b) **False.** Calcification is rare in the walls of veins, possibly because of the high CO<sub>2</sub> content of venous blood and the low pH.
- c) **False.** The calcification which occurs in old tuberculous lesions is dystrophic calcification. It occurs in tuberculous lesions because of the high fat content of caseous pus. This is due to the high lipid content of the M. tuberculosis which is liberated from the bacillus when it dies.
- d) **False.** Calcification certainly occurs in atheromatous plaques but this is also dystrophic in nature. Calcium is deposited because of the high concentration of lipid in atheroma.
- e) **True.** The cornea is frequently affected and the condition can be discovered during life by slit lamp examination. (Ref: Smiddy)

**Q. Osteoporosis differs from osteomalacia in that:**

- a) the radiographic density of the skeleton is reduced in the former and not the latter
- b) the remaining bone in the former presents a normal histological appearance
- c) major changes occur in the epiphyses in the former
- d) pseudofractures are commoner in the former than the latter
- e) excess osteoid tissue is present in the former

Ans.

- a) **False.** This is one of the cardinal changes in both conditions. It is a reflection of the decrease in the mass of calcified bone. In osteomalacia usually due to vitamin D deficiency, there is a derangement of the mineralisation of bone, osteoid is laid down but is not calcified. In osteoporosis the bone mass is reduced. This is a normal age related phenomenon approximately 0.7% of bone being lost per year after the attainment of the peak bone mass in young adult life.
- b) **True.** Osteoporosis, commonly observed following the menopause, is associated with a decrease in the total amount of bone, although the cellular composition of the remaining bone is normal as is the degree of mineralisation. Two general theories have been advanced to account for the development of osteoporosis, a decreased rate of new bone formation or enhanced bone resorption. Additional factors are the diminishing function of the osteoblasts with increasing age and in postmenopausal women oestrogen deficiency.
- c) **False** Changes in the epiphyses are characteristic of osteomalacia if its onset occurs before the epiphyses fuse as in rickets. Osteomalacia is caused by vitamin D deficiency and is associated with a failure of mineralisation of the osteoid and the cartilage of the epiphyseal growth plate in childhood. Radiological examination of affected long bones shows wide, irregular fuzzy, cupped metaphyses, thin bony cortices and the late appearance of epiphyseal centres.
- d) **False** Whilst fractures are common in established osteoporosis, pseudofractures, otherwise known as Looser's zones are characteristic of osteomalacia. Radiologically they are radiotranslucent lines which lie either at right angles or obliquely to the cortical outlines of the bones and often traverse them. They are commonly bilateral and symmetrical and are most frequently found in the axillary margins of the scapula and the neck of the femora.
- e) **False** Excess osteoid is the characteristic feature of osteomalacia. Calcification, however fails to occur in the absence of vitamin D.

**Q. Urinary hydroxyproline excretion may be Increased In:**

- |                                | Usually mild and<br>transient | Often severe and progressive |
|--------------------------------|-------------------------------|------------------------------|
| a) Paget's disease of bone     | T                             |                              |
| b) Cushing's syndrome          | F                             |                              |
| c) hypopituitarism in children | F                             |                              |
| d) hyperthyroidism             | T                             |                              |
| e) extensive fractures         | T                             |                              |

(Ref: Robbins & Cotran-9<sup>th</sup>, P-71)

**Explanation:**

When collagen is destroyed it is first degraded into soluble peptides containing the amino acid hydroxyproline. Most of the hydroxyproline is then degraded into carbon dioxide and urea but a small percentage circulates in the plasma to be excreted in the urine. Although the relationship between hydroxyproline excretion and bone resorption is not as simple as first appeared elevated values are normally taken as evidence that such a change is taking place.

In normal circumstances 8 to 10% of the hydroxyproline in the dietary gelatin and collagen appears in the urine and in addition recently synthesized collagen also contributes to the total urinary hydroxyproline.

In Paget's disease, which is a primary disorder of skeletal remodelling, the rapid turnover of bone leads to high urinary levels of hydroxyproline whereas in Cushing's disease attrition of the bone matrix leads to generalized osteoporosis. Weakening of the vertebral bodies produces bulging of the intervertebral discs giving rise to the classical radiological appearance of 'codfish' vertebrae but no rise in the urinary hydroxyproline value occurs because the bone matrix remains normal.

Q. The following conditions may be described as metabolic bone disease:

- a) osteoporosis
  - b) Paget's disease
  - c) osteomalacia
  - d) osteopetrosis
  - e) osteitis fibrosa cystica

Ans

- a) True** Albright defined metabolic bone disease as one in which a generalized disorder of bone arises as a consequence of a disturbance in general body metabolism. All bones are therefore involved although some may exhibit more pronounced changes than others. Osteoporosis fits into Albright's definition since there is an overall loss of bone mass even though that remaining retains its normal cellular appearance and degree of mineralisation.

**b) False** Paget's disease is not a metabolic bone disease. It is a condition of unknown aetiology, although possibly due to a slow virus infection caused by a paramyxovirus in which periods of osteoclastic activity are followed by bone formation. In about 15% of patients only a single bone is involved. In the remainder the condition is polyostotic chiefly involving the pelvis, spine and skull. The affected bone is typically enlarged with thick coarsened corticoid and cancellous bone.

**c) True** This change is accompanied histologically by decreased mineralisation and the presence of excess osteoid. Radiologically typical changes occur in the epiphyses as in rickets and in many patients pseudofractures known as Looser's zones occur. These are linear zones of translucency, cutting across at right angles to and usually affecting only one cortex.

**d) True** This is a hereditary disorder characterized by osteoclast dysfunction resulting in diffuse symmetrical skeletal sclerosis. The bones become grossly thickened and lack a medullary canal. The bone which is formed is not remodelled and tends to be woven so that the bone becomes brittle. Owing to the absence of the medullary cavity, extramedullary haemopoiesis causes hepatosplenomegaly.

**e) True** Radiological examination of the bone in this condition shows cyst formation and areas of bone erosion. Histologically the affected bone shows marked osteoclastic activity and secondary fibrosis. Microfractures followed by haemorrhages occur, producing the so-called 'red bone tumours' due to the fibrous tissue and the deposition of haemosiderin.

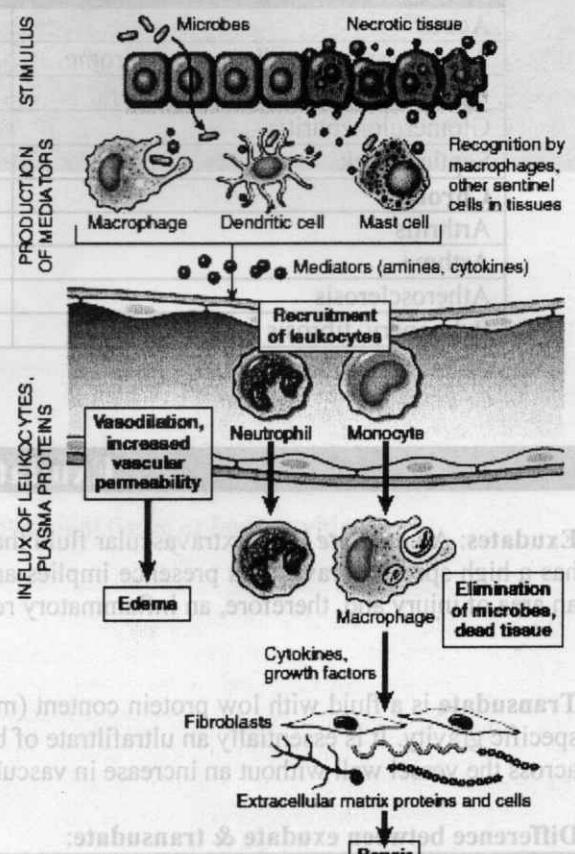
## INFLAMMATION

Inflammation is a response of vascularized tissues to infections and damaged tissues that brings cells and molecules of host defense from the circulation to the sites where they are needed, in order to eliminate the offending agents.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-69)

The typical inflammatory reaction develops through a series of sequential steps:

- The offending agent, which is located in extravascular tissues, is recognized by host cells and molecules.
- Leukocytes and plasma proteins are recruited from the circulation to the site where the offending agent is located.
- The leukocytes and proteins are activated and work together to destroy and eliminate the offending substance.
- The reaction is controlled and terminated.
- The damaged tissue is repaired.



**Fig: Sequence of events in an inflammatory reaction.**  
Macrophages and other cells in tissues recognize microbes and damaged cells and liberate mediators, which trigger the vascular and cellular reactions of inflammation.

■ **Classification:** Inflammation is 2 types.

1. Acute inflammation
2. Chronic inflammation

**Table 3-2 Features of Acute and Chronic Inflammation**

Feature	Acute	Chronic
Onset	Fast: minutes or hours	Slow: days
Cellular infiltrate	Mainly neutrophils	Monocytes/macrophages and lymphocytes
Tissue injury, fibrosis	Usually mild and self-limited	Often severe and progressive
Local and systemic signs	Prominent	Less

(Ref: Robbins & Cotran-9<sup>th</sup>, P-71)

### Diseases Caused by Inflammatory Reactions:

Disorders	Cells and Molecules Involved in Injury
<b>Acute</b>	
Acute respiratory distress syndrome	Neutrophils
Asthma	Eosinophils; IgE antibodies
Glomerulonephritis	Antibodies and complement; neutrophils, monocytes
Septic shock	Cytokines
<b>Chronic</b>	
Arthritis	Lymphocytes, macrophages; antibodies?
Asthma	Eosinophils; IgE antibodies
Atherosclerosis	Macrophages; lymphocytes
Pulmonary fibrosis	Macrophages; fibroblasts

(Ref: Robbins & Cotran-9<sup>th</sup>, P-71)

## Exudate & Transudate

**Exudates:** An **exudate** is an extravascular fluid that has a high protein concentration, contains cellular debris, and has a high specific gravity. Its presence implies an increase in the normal permeability of small blood vessels in an area of injury and, therefore, an inflammatory reaction.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-73)

**Transudate** is a fluid with low protein content (most of which is albumin), little or no cellular material, and low specific gravity. It is essentially an ultrafiltrate of blood plasma that results from osmotic or hydrostatic imbalance across the vessel wall without an increase in vascular permeability.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-73)

### Difference between exudate & transudate:

Traits	Exudate	Transudate
<b>1. Total protein</b>	High as in plasma	Less than 10 gm/L.
<b>2. Distribution of protein</b>	As in plasma	Nearly all albumin
<b>3. Fibrinogen</b>	Present if clots Spontaneously	Not present, no tendency to clot.
<b>4. Sp. gravity</b>	High ( $> 1.020$ )	Low ( $< 1.012$ )
<b>5. Cells</b>	Plenty polymorphs	Few mesothelial cells
<b>6. Cause</b>	Increased vascular Permeability	Hydrostatic imbalance across vascular endothelium.
<b>7. Occurrence</b>	Inflammatory condition	Non- inflammatory condition e.g. Nephrotic syndrome.

## Question Bank

**Q. Inflammatory exudate is formed due to (BSMMU –Residency - MD/MS, Basic science, Paediatrics, Dentistry – March '19)**

- a) increased hydrostatic pressure
- b) decreased colloidal osmotic pressure
- c) increased vascular permeability
- d) vasodilatation
- e) leakage of fluid, proteins and blood cells

Ans. a) T b) F c) T d) F e) T

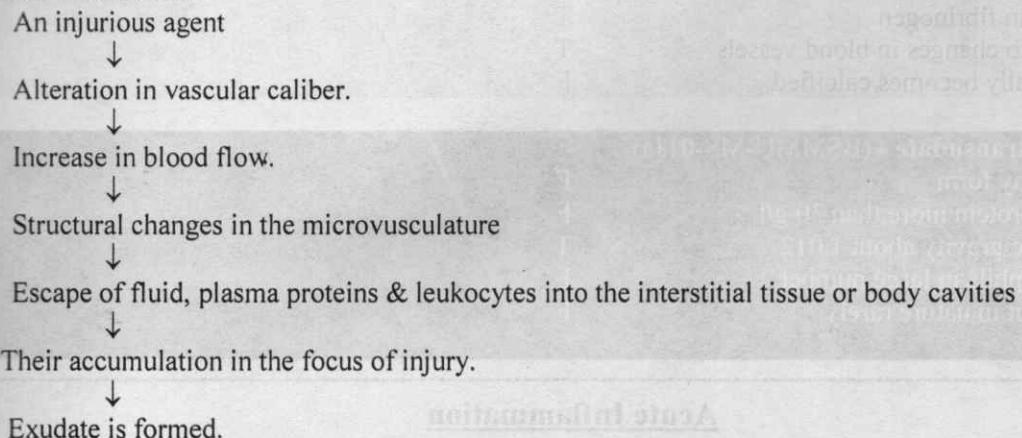
(Ref. Prof Khaleque page 22)

**Q. Acute inflammatory exudates:** (BSMMU – M. Phil, Diploma (Non-Residency)–March-2012, DMC & others – MS – March-2012)

- |                                       |   |
|---------------------------------------|---|
| a) contains many eosinophils          | F |
| b) has protective function            | T |
| c) is rich in fibrinogen              | T |
| d) is due to changes in blood vessels | T |
| e) eventually becomes calcified       | F |

#### HELP LINK:

##### Formation of exudates:



##### Types of exudates:

1. Fluid exudate
2. Cellular exudate

##### Cellular exudates:

- Mostly neutrophils and monocytes.
- Lymphocytes, eosinophils, basophils, platelets and RBCs may be present.
- Neutrophils is the hall mark of acute inflammation.

#### ■ Benefits of exudates:

##### A. Fluid exudates:

1. Dilution of irritant substances.
2. Exudates carry inflammatory cells & natural anti-bacterial substances like opsonin, complement, specific immunoglobulins.
3. Drugs & antibiotics appear at the site of action from the circulation through the exudates.
4. It contains fibrin which has 3 main functions-
  - It forms an union between the cut/damaged tissues.
  - It may form a barrier against bacterial invasion.
  - It aids phagocytosis.
5. Nutrition to the greatly increased cells.
6. Low pH due to lactic acid formation (by injured cells & nerves). So, inhibits bacterial growth.
7. Promotion of immunity: by carrying Ag to local lymphnode and inducing immune response.

##### B. Cellular exudates:

1. Neutrophils, macrophages- ingest foreign particles, bacteria & cell debris.
2. Plasma cells secretes immunoglobulins.

**Harmful effects of fluid exudate:**

1. It acts as a splendid medium for bacterial growth due to high protein content.
2. An excess of fibrin may lead to adhesion.
3. Presence of chemical mediator like prostaglandin, 5HT, bradykinin causes initiation of nerve endings and results in pain.

**Q. Acute Inflammatory exudate (BSMMU – MD/MS (Residency) – January, 2011)**

- |                                       |   |
|---------------------------------------|---|
| a) contains many eosinophils          | F |
| b) has protective function            | T |
| c) is rich in fibrinogen              | T |
| d) is due to changes in blood vessels | T |
| e) eventually becomes calcified       | F |

**Q. Character of transudate - (BSMMU-MS-01Ja)**

- |                                    |   |
|------------------------------------|---|
| a) Clot may form                   | F |
| b) Total protein more than 30 g/l. | F |
| c) Specific gravity about 1.012    | T |
| d) Neutrophils in large number     | F |
| e) Purulent in nature rarely       | F |

**Acute Inflammation**(Ref: Robbins & Cotran-9<sup>th</sup>, P-73)  
Exudate is formed**Q. Features associated with acute inflammation are (BSMMU – Non-Residency – MD, MS, Basic science, Dentistry – July' 16)**

- |                                 |   |
|---------------------------------|---|
| a) increased ESR                | T |
| b) increased monocyte count     | F |
| c) increased IgG                | F |
| d) toxic granules in neutrophil | T |
| e) increased C-reactive protein | T |

**Help link:**

**Definition:** Acute inflammation is the inflammation which is rapid in onset (typically minutes) and is of short duration, lasting for hours or a few days; its main characteristics are the exudation of fluid and plasma proteins (edema) and the emigration of leukocytes, predominantly neutrophils (also called polymorphonuclear leukocytes).

(Ref: Robbins & Cotran-8<sup>th</sup>, P-44)**Cardinal signs:**

1. Rubor (Redness): due to hyperaemia or increased blood flow
2. Tumor (Swelling): due to formation of exudate
3. Calor (Heat): due to hyperaemia
4. Dolor (Pain): due to bradykinin
5. Functio laesa (Loss of function)

(Ref: Robbins & Cotran-9<sup>th</sup>, P-71+Text Book of Harsh Mohan of pathology)**Component of acute inflammation:**

Acute inflammation has three major components:

- (1) alterations in vascular caliber that lead to an increase in blood flow.
- (2) structural changes in the microvasculature that permit plasma proteins and leukocytes to leave the circulation, and
- (3) emigration of the leukocytes from the microcirculation, their accumulation in the focus of injury, and their activation to eliminate the offending agent.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-73)

**Beneficiary effects:**

1. Without inflammation, infection would remain unchanged.
2. Without inflammation, wounds would never heal.
3. Injured tissues & organs might remain as permanent defect.

**Harmful effects:**

1. It may lead to disfiguring scar.
2. Formation of fibrous bands may limit the mobility of a joint.
3. Formation of large scar tissue in an organ, may impair the function of the organ.
4. Immune mediated hypersensitivity reaction may cause generalized inflammation leading to massive exudation & shock.
5. Leukocyte products released, causes endothelial cell injury & tissue damage.

**Events of acute inflammation**

**Q** Events that occur early in acute inflammation are (BSMMU – Residency – MD, MS, Basic Science March '18)

- a) emigration of neutrophils
- b) production of antibody by plasma cells
- c) proliferation of blood vessels
- d) dilatation of blood vessels
- e) synthesis of C reactive protein

Ans. a) T b) F c) F d) T e) T

**Help link:****Events of acute inflammation:**

**A. Vascular events:** (Reactions of Blood Vessels In Acute Inflammation)

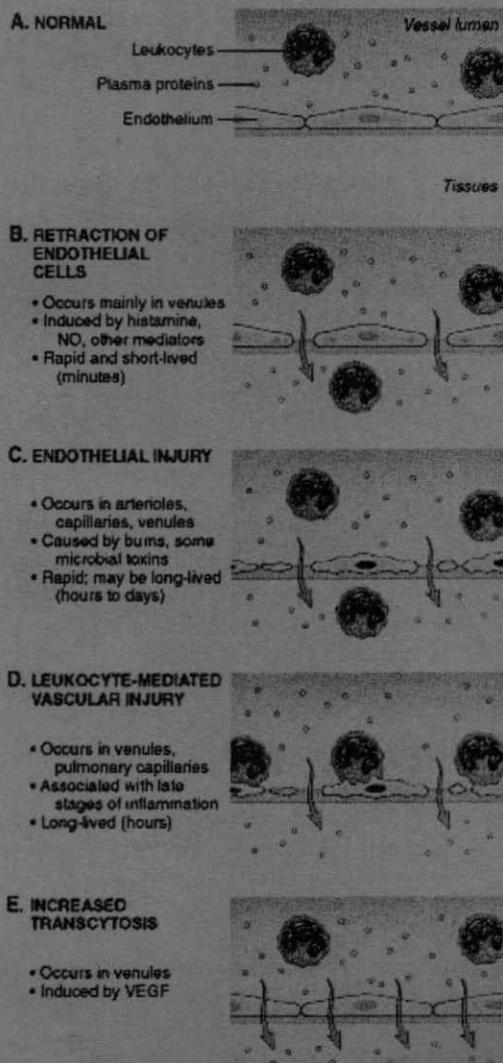
**a) Changes in Vascular Flow and Caliber:**

- **Vasodilation** is induced by the action of several mediators, notably histamine, on vascular smooth muscle. It is one of the earliest manifestations of acute inflammation. Vasodilation first involves the arterioles and then leads to opening of new capillary beds in the area.
- **Increase in blood flow.** Vasodilation results in increased blood flow, which is the cause of heat and redness (erythema) at the site of inflammation.
- **Increased permeability of the microvasculature**, with the outpouring of protein-rich fluid into the extravascular tissues
- **Stasis:** - Loss of fluid & increased vessel diameter lead to slower blood flow.
  - Concentration of red cells.
  - Increased viscosity of the blood.

**b) Increased Vascular Permeability (Vascular Leakage) leading to the escape of a protein-rich fluid**

(exudate) into the extravascular tissue, causing edema.

- Hallmark of acute inflammation



**M/A:**

1. Contraction of endothelial cells resulting increased inter-endothelial spaces
  - Elicited by histamin, bradykinin, leukotrienes, substance P etc.
  - Immediate transient response
    - short lived (15-30 minutes)
  - Delayed prolonged leakage (several hours or even days)
    - Mild injury ( after burn, x-irradiation or UV ray, bacterial toxin)
    - Late-appearing sunburn

**FIGURE:** Principal mechanisms of increased vascular permeability in inflammation, and their features and underlying causes. NO, nitric oxide; VEGF, vascular endothelial growth factor.

\*Info: Mononuclear cell: macrophage, lymphocytes, plasma cell.

2. Endothelial injury resulting in endothelial cell necrosis & detachment
  - direct damage to endothelium (Burn, action of microbes)
  - Neutrophils that adhere to endothelium during inflammation may also injure endothelium.
3. Transcytosis: Increased transport of fluids and protein through the endothelial cell. VEGF promote vascular leakage.

**B. Cellular events:**

- Leukocyte Recruitment to Sites of Inflammation
- Leukocyte Adhesion to Endothelium
- Leukocyte Migration Through Endothelium
- Chemotaxis of Leukocytes
- Phagocytosis and Clearance of the Offending Agent

(Ref: Robbins & Cotran-9<sup>th</sup>, P-73-76)

[In short, Transient vasoconstriction → Vasodilation → Increased blood flow → Slowing of circulation (due to permeability) → Stasis → Initiation of cellular events]

**Q. Acute inflammation is characterized by:** (BSMMU - M. Phil, Diploma – July '10)

- |   |   |
|---|---|
| a) Alteration in vascular caliber that lead to an increased flood flow                                | T |
| b) Structural changes in microvasculature that permit plasma protein & leukocyte to leave circulation | T |
| c) Tissue destruction and attempts of healing   | F |
| d) Mononuclear cell infiltration  | F |
| e) Leukocyte emigration from microcirculation   | T |

**Q. Oedema in inflammation occurs due to:** (BSMMU – MD – January, 2010)

- |  |   |
|--|---|
| a) endothelial contraction                             | T |
| b) increased viscosity of blood                        | F |
| c) action of interleukin I on endothelial cell         | T |
| d) increased hydrostatic pressure                      | T |
| e) injury of endothelial cells by activated leucocytes | T |

[Ref: Prof. Khaleque, P-15]

**Q. During inflammation, formation of endothelial gaps in venules is mediated by:** (BSMMU – MD/MS - January, 2009)

- |   |   |
|---|---|
| a) vascular endothelium derived growth factor | F |
| b) toxins                                     | F |
| c) leukotrienes                               | T |
| d) histamine                                  | T |
| e) bradykinin                                 | T |

**HELP LINK:**

- Formation of endothelial gaps in venules: (endothelial cell contraction)
- Most common.
- Elicited by histamine, bradykinin, leukotrienes, the neuropeptide substance P etc.
- Response is reversible and short-lived (15 - 30 min).
- It is known as *immediate transient response*.
- Binding of mediators such as histamine, to their receptors on endothelial cells activates intracellular signaling pathways → It leads to Mediated by phosphorylation of contractile and cytoskeletal proteins, myosin. These proteins contract, leading to contraction of endothelial cells & separation of intercellular junctions.
- Cytokines (IL-1, TNF, IFN- $\gamma$ ) also increase vascular permeability by inducing a structural reorganization of cytoskeleton, so that the endothelial cells retract from each other. This response is delayed & long lived.

(Ref: Robbins & Cotran-7<sup>th</sup>, P-52)

## ■ In acute inflammation, vasodilatation: (BSMMU – MD/MS - January, 2008)

- |   |                |
|---|----------------|
| a) is an initial transient phenomenon     | F              |
| b) may sometimes precede vasoconstriction | T              |
| c) leads to stasis                        | T              |
| d) is partly due to histamine             | T              |
| e) is also known as congestion            | F (Hyperaemia) |

**HELP LINK:**

## ■ Major components of acute inflammation:

Vascular responses:

- Changes in vascular caliber leading to increase in blood flow.
- Increase vascular permeability to plasma proteins & leukocytes.

- Cellular response: Emigration of the leukocytes from the micro-circulation and their accumulation in the focus of injury.

Vascular changes:■ Changes in the calibre of blood vessels:

- Initial vasoconstriction: The earliest response to acute injury is the constriction of small blood vessels which persist seconds to minute. This vasoconstriction partly due to direct mechanical stimulation and partly may be neurogenic in origin.

- Persistent vasodilatation: The initial vasoconstriction phase is followed by massive vasodilatation in the arterioles and capillaries in the injured area, and persists for the duration of inflammatory process. Thus comes about increased blood flow which is the cause of heat and redness.

■ Changes in the vessels wall and the flow of blood:

- Slowing of circulation: The first change is an increase in blood velocity due to arteriolar dilatation. This phase is short lived and is followed by a slowing of circulation. This slowing of circulation is brought about by increased permeability of the microvasculature with outpouring of protein rich fluid into extra-vascular tissues. The latter results in concentration of red cells in small vessels and increased viscosity of the blood, reflected by the presence of dilated small vessels packed with red cells termed as stasis.

- Stasis: As stasis develops there is peripheral orientation of leukocytes principally neutrophil along the vascular endothelium a process called leukocytic margination. Leukocytes then stick to the endothelium, at first transiently, then more avidly and soon afterward they migrate through the vascular wall into the interstitial tissue.

(Ref: WALTER &amp; ISRAEL)

**Q. In acute inflammation, increased vascular permeability due to endothelial contraction is mediated by -** (BSMMU - M. Phil, Diploma July-06)

- |                                 |   |
|---------------------------------|---|
| a) Bradykinin                   | T |
| b) Prostaglandin E <sub>2</sub> | T |
| c) Histamine                    | T |
| d) Leukotriene C <sub>4</sub>   | T |
| e) Leukotriene B <sub>4</sub>   | F |

**Q. Acute inflammation – [MD/MS (DMC) - 04Ja]**

- |   |   |
|---|---|
| a) is a reaction of short duration                    | T |
| b) is characterized by proliferative tissue reaction. | F |
| c) is non-specific in nature                          | T |
| d) usually heals by complete resolution               | T |
| e) always precede chronic inflammation                | F |

**Q. Increased vascular permeability in acute inflammation has the following effects- (BSMMU-MS-04Ja)**

- |   |   |                                       |
|---|---|---------------------------------------|
| a) Local redness                              | F | [Ref: Robbins-9 <sup>th</sup> , P-74] |
| b) Increase in temperature                    | F |                                       |
| c) Formation of fluid exudate                 | T |                                       |
| d) Swelling                                   | T |                                       |
| e) Increased viscosity of blood at local site | T |                                       |

**Q. The acute inflammation increased permeability of venules is mediated by- (BSMMU-Sur-04Ja)**

- |                                 |   |
|---------------------------------|---|
| a) Leukotriene D <sub>4</sub> . | T                                       |
| b) Histamine                    | T                                       |
| c) Bradykinin                   | T                                       |
| d) Prostaglandin D <sub>2</sub> | T [Ref: Robbins-9 <sup>th</sup> , P-84] |
| e) Lipoxin                      | F                                       |

**Help link:**

**The acute inflammation increased permeability of venules is mediated by**

- Histamine, Leukotrienes, Bradykinin, Neuropeptide, Subs. P
- IL-1, TNF, IFN-γ, VEGF

**Q. Markers of inflammation include - (BSMMU-MD-03Ju)**

- |                              |   |
|------------------------------|---|
| a) C- reactive protein       | T |
| b) High uric acid            | F |
| c) High ESR                  | T |
| d) High alkaline phosphatase | F |
| e) Low platelet count        | F |

**Q. During acute inflammatory response- (BSMMU-MD-01Ja)**

- |  |                               |
|--|-------------------------------|
| a) Histamine causes vasodilatation                   | T                             |
| b) The exuded fibrin is formed by fibroblasts        | F                             |
| c) Margination of monocytes is an early event        | F                             |
| d) Red cell diapedesis is a passive phenomena        | T [Ref: Prof. Khaleque, P-16] |
| e) Complement components may act as chemoattractant. | T                             |

**Q. The following types of cell function primarily in the initial phases of inflammation: (MD/MS (DMC)-01Ja)**

- |                                 |   |
|---------------------------------|---|
| A. Eosinophils                  | F |
| B. Basophils                    | F |
| C. T- lymphocytes               | F |
| D. Polymorphonuclear leucocytes | T |
| E. Plasma cells                 | F |

## Fate of acute inflammation

**Q. Outcomes of acute inflammation are (BSMMU – Residency - Dentistry – March' 19)**

- a) complete resolution
- b) neoplastic transformation
- c) healing by fibrosis
- d) dysplastic changes
- e) progression to chronic inflammation

Ans. a) T b) F c) T d) F e) T

**Help link:**

■ **Outcomes/ Fates of acute inflammation:**

1. **Complete resolution:** In a perfect world, all inflammatory reactions, once they have succeeded in neutralizing and eliminating the injurious stimulus, should end with restoration of the site of acute inflammation to normal. This is called **resolution** and is the usual outcome when the injury is limited or short-lived or when there has been little tissue destruction and the damaged parenchymal cells can regenerate. Resolution involves removal of cellular debris and microbes by macrophages, and resorption of edema fluid by lymphatics.

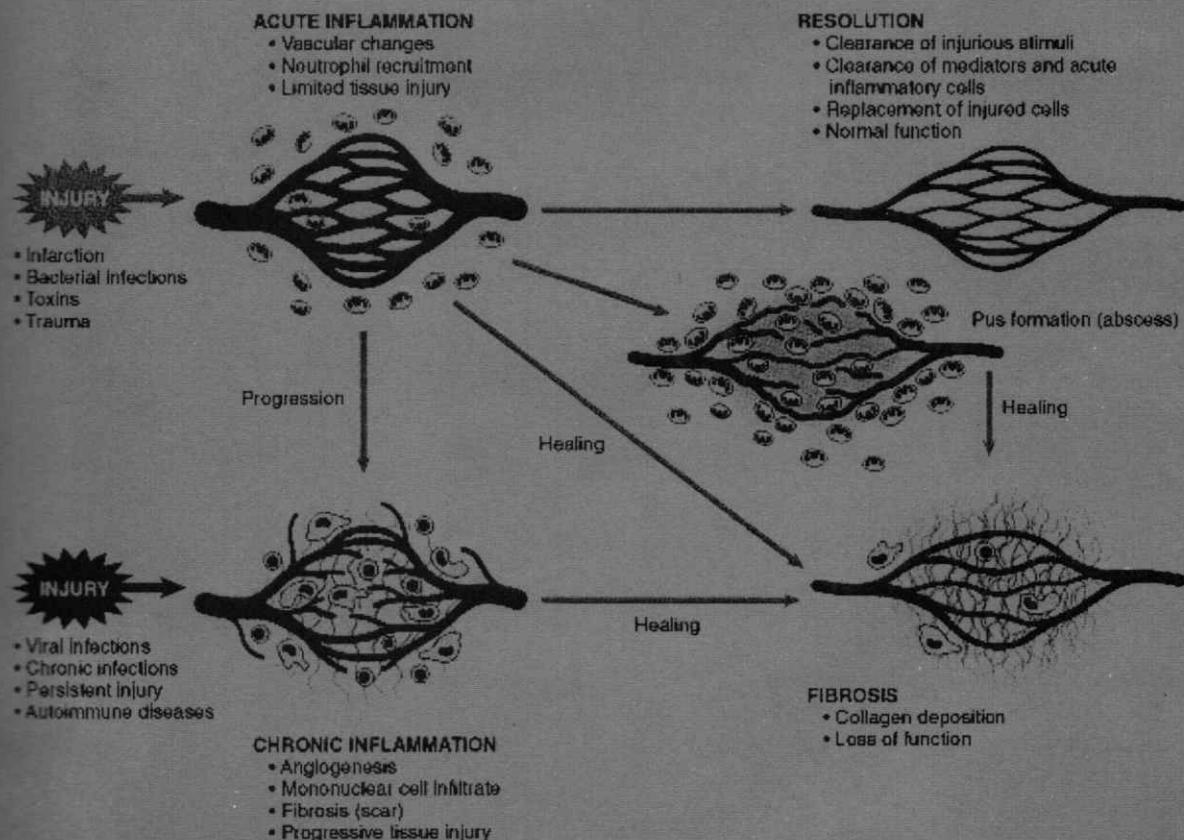
2. **Healing by connective tissue replacement (fibrosis):** It occurs -

- after substantial tissue destruction
- when inflammatory injury involves tissues that are incapable of regeneration
- when there is abundant fibrin exudation in tissue or serous cavities (pleura, peritoneum)

In all these situations, connective tissue grows into the area of damage or exudate, converting it into a mass of fibrous tissue—a process also called *organization*.

3. **Chronic inflammation:** This may follow acute inflammation, or the response may be chronic from the onset.

(Ref: Robbins & Cotran-8<sup>th</sup>, P-66)



**FIGURE:** Outcomes of acute inflammation: resolution, healing by fibrosis, or chronic inflammation. The components of the various reactions and their functional outcomes are listed.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-92)

**Q. Outcomes of acute inflammation are (BSMMU – Residency – Dentistry – March' 18)**

- a) resolution
- b) organization
- c) fibrosis
- d) embolization
- e) vasodilation

**Ans. a) T b) F c) T d) F e) F**

**Q. Fates of acute inflammation are (BSMMU – Residency - Dentistry - March' 17)**

- a) chronic inflammation
- b) embolization
- c) scar formation
- d) malignant transformation
- e) resolution

**Ans. a) T b) F c) T d) F e) T**

### Chronic inflammation

**■ Definition:** Chronic inflammation is a response of prolonged duration (weeks or months) in which inflammation, tissue injury, and attempts at repair coexist, in varying combinations.

**Example:** Rheumatoid arthritis, atherosclerosis, tuberculosis and chronic lung diseases.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-93)

**Histological features:** Chronic inflammation is characterized by:

- **Infiltration with mononuclear cells**, which include macrophages, lymphocytes, and plasma cells.
- **Tissue destruction**, induced by the persistent offending agent or by the inflammatory cells
- **Attempts at healing** by connective tissue replacement of damaged tissue, accomplished by proliferation of small blood vessels (*angiogenesis*) and, in particular, *fibrosis*.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-93-94)

**Q. Features of chronic inflammation are (BSMMU – Non-Residency – MD, MS, Basic science & Dentistry – July' 18)**

- a) exudate
- b) edema
- c) tissue destruction
- d) fibrosis
- e) suppuration

**Ans. a) F b) F c) T d) T e) F**

**Help link:**

Features of Chronic inflammation:

1. Infiltration with mononuclear cells
2. Tissue destruction
3. Attempts at healing & fibrosis

(Ref: Robbins 9<sup>th</sup>, 93-94)

**Q. Hall mark of chronic inflammation (BSMMU – Diploma – Dentistry-July' 16)**

- a) tissue destruction
- b) neutrophil
- c) eosinophil
- d) fibrosis
- e) basophil

**Ans. a) T b) F c) F d) F e) F**

**Help link:**

**Hall mark of chronic inflammation:**

- Macrophage
- Plasma cell
- Lymphocyte

**Q. Morphologic features of chronic inflammation are (BSMMU –Residency - MD/MS, Basic science – March' 14)**

- |                                  |   |
|----------------------------------|---|
| a) infiltration with macrophages | T |
| b) fibrosis                      | T |
| c) presence of exudate           | F |
| d) infiltration with neutrophils | F |
| e) plasma cell infiltration      | T |

**Q. In chronic inflammation- (MD/MS (DMC)-03Ja)**

- |   |   |
|---|---|
| a) Macrophage plays the central role                    | T                                       |
| b) Tissue destruction is the hall mark                  | T                                       |
| c) Complete resolution often occurs                     | T [Ref: Robbins-9 <sup>th</sup> , P-92] |
| d) Tissue response is sometimes specific                | T                                       |
| e) Healing is accomplished by angiogenesis and fibrosis | T                                       |

### Cells in Chronic Inflammation

**Q. Activated macrophages produce (BSMMU – Non-Residency – MD, MS, Paediatrics, Basic Science – July'**

- 19
- |                  |
|------------------|
| a) TNF $\alpha$  |
| b) IL-1          |
| c) INF- $\gamma$ |
| d) IL-12         |
| e) IL-17         |

Ans. a) T b) T c) F d) T e) F

**Help Link:**

**Cells in Chronic Inflammation:**

Cells	Mediators
<b>1. Activated Macrophage</b>	i. Enzymes: <ul style="list-style-type: none"> <li>• Neutral Proteases</li> <li>• Plasminogen activator</li> <li>• Acid hydrolases</li> <li>• Remodeling collagenase</li> </ul> ii. Plasma proteins: <ul style="list-style-type: none"> <li>• Complement component (C1-C5)</li> <li>• Coagulation Factors (Factor- V &amp; VIII)</li> </ul> iii. Eicosanoids iv. Reactive oxygen metabolites v. Cytokines, chemokines (IL-1, TNF- $\alpha$ ) vi. Nitric oxide vii. Growth Factors (FGF, PDGF, EGF, TGF- $\beta$ ) viii. Angiogenesis factors (VEGF, angiopoietin, FGF)
<b>2. Lymphocyte</b>	<ul style="list-style-type: none"> <li>• Lymphokines</li> <li>• INF-<math>\gamma</math></li> </ul>
<b>3. Eosinophil</b>	<ul style="list-style-type: none"> <li>• Major basic protein</li> </ul>
<b>4. Mast cell</b>	<ul style="list-style-type: none"> <li>• TNF-<math>\alpha</math></li> </ul>

(Ref: Robbin's Basic Pathology-9<sup>th</sup>Ed)

**Q. Cells that participate in chronic inflammation (BSMMU – Residency – Dentistry – March' 18)**

- a) macrophage
- b) neutrophil
- c) eosinophil
- d) fibroblast
- e) lipoblast

Ans. a) T b) F c) T d) T e) F

## Lysosomal enzymes

**Q. Following enzymes are found in lysosome: (BSMMU – M. Phil, Diploma (Non-Residency) – IIJu, DMC & others – MD – IIJu)**

a) ribonuclease	T
b) deoxyribonuclease	T
c) myeloperoxidase	F
d) oxidase	F
e) phosphatase	T

### HELP LINK:

Lysosomes are the membrane bound vesicular organelles found throughout the cytoplasm. The lysosomes are formed by Golgi apparatus. The enzymes synthesized in rough endoplasmic reticulum are processed and packed in the form of small vesicles in the Golgi apparatus. Then, these vesicles are pinched off from Golgi apparatus and become the lysosomes.

Among the organelles of the cytoplasm, the lysosomes have the thickest covering membrane. The membrane is formed by bilayered lipid material. Many small granules are present in the lysosome. The granules contain the hydrolytic enzymes.

**Types of Lysosomes**— Lysosomes are two types:

- **Primary lysosome:** It is the one that is pinched off from Golgi apparatus. In spite of having the hydrolytic enzymes, the primary lysosome is inactive.
- **Secondary lysosome:** It is the active lysosome that is formed by the fusion of a primary lysosome with phagosome or endosome.

### Functions of Lysosomes:

Two mechanisms are involved in the lysosomal functions:

- **Heterophagy:** digestion of extracellular materials engulfed by the cell via endocytosis.
- **Autophagy:** digestion of intracellular materials such as worn out cytoplasmic organelles.

Lysosomes are often called 'garbage system' of the cell because of their degradation activity.

About 50 different hydrolytic enzymes, known as acid hydroxylases are present in the lysosomes:

Lysosomes execute their functions through these enzymes which include:

- Proteases which hydrolyze the proteins into amino acids
- Lipases which hydrolyze the lipids into fatty acids and glycerides
- Amylases which hydrolyze the polysaccharides into glucose
- Nucleases which hydrolyze the nucleic acids into mononucleotides.

## Morphological types of inflammation

### Morphological types of inflammation:

1. **Serous inflammation:** It is marked by the outpouring of a thin fluid that may be derived from the plasma or from the secretions of mesothelial cells lining the peritoneal, pleural, and pericardial cavities.
  - Accumulation of fluid in the cavities is called an *effusion*. eg. pleural effusion.
  - The skin blister resulting from a burn or viral infection represents a large accumulation of serous fluid, either within or immediately beneath the epidermis of the skin

2. **Fibrinous inflammation:** With greater increase in vascular permeability, large molecules such as fibrinogen pass the vascular barrier, and fibrin is formed and deposited in the extracellular space. A fibrinous exudate is characteristic of inflammation in the lining of body cavities, such as the meninges, pericardium and pleura. eg. fibrinous pericarditis after acute MI.
3. **Suppurative/purulent inflammation:** This type of inflammation is characterized by the production of large amounts of pus or purulent exudate consisting of neutrophils, liquefactive necrosis, and edema fluid. Certain bacteria (e.g., staphylococci) produce this localized suppuration and are therefore referred to as *pyogenic* (pus-producing) bacteria. A common example of an acute suppurative inflammation is acute appendicitis.
4. **Ulcers:** An ulcer is a local defect, or excavation, of the surface of an organ or tissue that is produced by the sloughing (shedding) of inflamed necrotic tissue. eg. Peptic ulcer of stomach or duodenum.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-90-91)

### Question Bank

**Q. Suppuration is mainly the result of the combined action of (BSMMU – Non-Residency – Dentistry – July' 19)**

- a) necrosis
- b) presence of lymphocytes
- c) collection of neutrophils
- d) accumulation of tissue fluid
- e) autolysis by gastric juice

Ans. a) T b) F c) T d) T e) F

**Q. Suppurative inflammation (BSMMU – Residency - MD, MS, Basic Science, Dentistry - March' 17)**

- a) is a consequence of infarction
- b) is seen in staphylococcal infection
- c) contains polymorphs
- d) is the early stage of gangrene
- e) usually heals by secondary intention

Ans. a) F b) T c) T d) F e) T

N.B: In initial stages of gangrene there will be either arterial obstruction or venous drainage causes coagulative type of necrosis followed by superimposed bacterial infection causes liquefactive necrosis.

**Q. Substances found in pus are (BSMMU – Residency - Dentistry - March' 17)**

- a) histiocytes
- b) dead bacteria
- c) live bacteria
- d) plasma cells
- e) eosinophils

Ans. a) T b) T c) T d) T e) F

**Help link:**

**Pus:** Pus is a purulent inflammatory exudate rich in leukocytes (mostly neutrophils), the debris of dead cells, and in many cases, microbes.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-73)

**Composition of pus:**

1. Dead & dying leukocytes.
2. Parenchymal tissue debris.
3. Inflammatory exudates: edema fluid & fibrin.
4. Living or dead organisms.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-73, 91)

**Formation of pus:** Infection by pyogenic organisms → Tissue necrosis → Profuse polymorphs infiltration →

The organisms kill many leukocytes (pus cell) → The necrotic material undergo softening by proteolytic enzymes released by dead leukocytes (keratolysis) & necrosed tissue (autolysis) → Formation of pus.

**Q. Pus contains:** (BSMMU-MS-01Ja)

- a) lipids
- b) fibrin
- c) collagen
- d) plasma cells
- e) polymorphonuclear leucocytes

Ans.

- a) **True** Lipids are present in pus. They are derived from the plasma lipoproteins and from cellular breakdown products. Cholesterol may be found in old pus.
- b) **True** Pus contains fibrin because the activation of the coagulation system by the Hageman factor converts plasma fibrinogen into fibrin. The Hageman factor, Factor XII in the international classification of plasma coagulation factors, may be activated by kallikrein.
- c) **False** Collagen is not a constituent of pus although its breakdown products may be present due to the activity of enzymes known as collagenases. During healing collagen is laid down by fibroblasts.
- d) **False** Plasma cells are not normally found in the pus formed as a result of acute inflammation. Chiefly they are found, together with lymphocytes, in the lymph nodes, spleen and gut but they are also present in the organised granulomas which form in 'chronic inflammatory' lesions such as those which develop in rheumatoid arthritis.
- e) **True** The major cellular component of pus consists of living or dead polymorphonuclear leucocytes. These cells, when living, destroy ingested microorganisms, if these are the cause of the acute, inflammatory process. Polymorphonuclear leucocytes are attracted to the site of an acute inflammatory reaction by a variety of chemotactic agents, one of the most potent of which in vitro is a lysate of the polymorphonuclear leucocytes themselves.

(Ref: Smiddy)

## CHEMOTAXIS

**Q. Chemotactic factors include -** (DMC – MD/ MS - January, 2010)

- |                                  |   |
|----------------------------------|---|
| a. C5a                           | T |
| b. H <sub>2</sub> O <sub>2</sub> | F |
| c. Leukotriene B4                | T |
| d. IL-8                          | T |
| e. NO                            | F |

### HELP LINK:

■ **Definition:** After exiting the circulation, leukocytes emigrate in tissues toward the site of injury by a process called **chemotaxis**, which is defined as locomotion oriented along a chemical gradient.

#### Chemoattractants/ Chemical factors:

Both exogenous and endogenous substances can act as chemoattractants.

- **Exogenous:** bacterial products, including peptides that possess an *N*-formylmethionine terminal amino acid, and some lipids.
- **Endogenous:** chemical mediators:
  - (1) *cytokines*, particularly those of the chemokine family (e.g., IL-8)
  - (2) *components of the complement system*, particularly C5a; and
  - (3) *arachidonic acid (AA) metabolites*, mainly leukotriene B<sub>4</sub> (LTB<sub>4</sub>).

■ **Process:** Chemotactic agents bind to specific seven-transmembrane G protein-coupled receptors on the surface of leukocytes.



Signals initiated from these receptors result in activation of second messengers that increase cytosolic calcium and activate small guanosine triphosphatases of the Rac/Rho/cdc42 family as well as numerous kinases.



These signals induce polymerization of actin, resulting in increased amounts of polymerized actin at the leading edge of the cell and localization of myosin filaments at the back.



The leukocyte moves by extending filopodia that pull the back of the cell in the direction of extension, much as an automobile with front-wheel drive is pulled by the wheels in front.



The net result is that leukocytes migrate toward the inflammatory stimulus in the direction of the gradient of locally produced chemoattractants. (**chemotaxis**).

(Ref: Robbins & Cotran-9<sup>th</sup>, P-77)

**Q. The chemotactic factors are:** (BSMMU - M. Phil, Diploma, July-09)

- |                                 |   |
|---------------------------------|---|
| a) Complement C5a               | T |
| b) Prostaglandin I <sub>2</sub> | F |
| c) Histamine                    | F |
| d) Interleukin 8                | T |
| e) Leukotrine B4                | T |

## PHAGOCYTOSIS

■ **Phagocytosis:** It is the process by which polymorphs & macrophages engulf particulate matters such as microbes, immune complex and tissue debris in order to kill or degrade them.

■ **Steps:** Phagocytosis involves three sequential steps:

- (1) *recognition and attachment* of the particle to be ingested by the leukocyte.
- (2) its *engulfment*, with subsequent formation of a phagocytic vacuole; and
- (3) *killing or degradation* of the ingested material.

**1. Recognition & attachment:**

- The phagocytosis of microbes & dead cells is initiated by recognition of the particles by receptors expressed on the leukocyte surface.
- *Mannose receptors, scavenger receptors, and receptors for various opsonins* all function to bind and ingest microbes.
- The efficiency of phagocytosis is greatly enhanced when microbes are opsonized by specific proteins (opsonins) for which the phagocytes express high-affinity receptors. Major opsonins are IgG antibodies, the C3b breakdown product of complement, and certain plasma lectins, notably mannose-binding lectin, all of which are recognized by specific receptors on leukocytes.

**2. Engulfment:** After a particle is bound to phagocyte receptors, extensions of the cytoplasm (pseudopods) flow around it, and the plasma membrane pinches off to form a vesicle (phagosome) that encloses the particle. The phagosome then fuses with a lysosomal granule, resulting in discharge of the granule's contents into the phagolysosome. During this process the phagocyte may also release granule contents into the extracellular space.

**3. Killing and degradation:** Microbial killing is accomplished largely by *Reactive oxygen species* (ROS, also called reactive oxygen intermediates) and *Reactive nitrogen species*, mainly derived from NO.

■ **O<sub>2</sub> dependent system:** Phagocytosis → O<sub>2</sub> consumption → glycogenolysis → glucose oxidation → production of O<sub>2</sub> metabolites (by activation of oxidase)

i. **H<sub>2</sub>O<sub>2</sub>-MPO-halide system:** (hydrogen peroxide - Myeloperoxide-halide system)

- Activation of NADPH oxidase (also called phagocyte oxidase)

- This enzyme oxidizes NADPH (reduced nicotinamide-adenine dinucleotide phosphate) and reduces oxygen to superoxide anion ( $O_2^\bullet$ ).
 
$$[2O_2 + NADPH \rightarrow 2O_2^\bullet + NADP + H^+]$$
  - $O_2^\bullet$  is then converted into hydrogen peroxide ( $H_2O_2$ ), mostly by spontaneous dismutation.  $[2O_2^\bullet + 2H^+ \rightarrow H_2O_2]$
  - $H_2O_2$  react with halide ( $Cl^-$ ) by myeloperoxidase & produce hypochlorite:
 
$$[H_2O_2 + Cl^- \rightarrow 'HO + HOCl']$$
  - Hypochlorohalide is a powerful bactericidal agent. It is a potent antimicrobial agent that destroys microbes by
    - by **halogenation** (in which the halide is bound covalently to cellular constituents) or
    - by **oxidation** of proteins and lipids (lipid peroxidation).
- ii.  $H_2O_2$  is also converted to hydroxyl radical ('OH), another powerful destructive agent.
- iii. **NO**, produced from arginine by the action of nitric oxide synthase (NOS), also participates in microbial killing. NO reacts with superoxide ( $O_2^\bullet$ ) to generate the highly reactive free radical peroxynitrite (ONOO'). These oxygen- and nitrogen-derived free radicals attack and damage the lipids, proteins, and nucleic acids of microbes as they do with host macromolecules.
- b. ***O<sub>2</sub>* independent system:** Microbial killing can also occur through the action of other substances in leukocyte granules.
- **Elastase** enzyme: contribute to microbial killing.
  - **Defensins**: cationic arginine-rich granule peptides that are toxic to microbes.
  - **Cathelicidins**: antimicrobial proteins found in neutrophils and other cells.
  - **Lysozyme**: hydrolyzes the muramic acid-N-acetylglucosamine bond, found in the glycopeptide coat of all bacteria.
  - **Lactoferrin**: an iron-binding protein present in specific granules.
  - **Major basic protein**: a cationic protein of eosinophils, which has limited bactericidal activity but is cytotoxic to many parasites.
  - **Bactericidal/permeability increasing protein**: binds bacterial endotoxin and is believed to be important in defense against some gram-negative bacteria.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-77-78)

#### Question Bank

**Q. Phagocytosis results in release of (BSMMU – Non-Residency – MD, MS, Basic Science & Dentistry – July '17)**

- a) TGF-β
- b) lysosomal products
- c) hydrogen peroxide
- d) interleukin
- e) arachidonic acid metabolites

Ans. a) F b) T c) T d) F e) F

**Q. After phagocytosis microorganisms are killed by: (BSMMU – M. Phil, Diploma (Non-Residency)–March-2012, DMC & others – MD/MS – March-2012)**

- |                          |   |
|--------------------------|---|
| a) myeloperoxidase alone | F |
| b) hydrogen peroxide     | T |
| c) lysozyme              | T |
| d) complement system     | F |
| e) immunoglobulins       | F |

**Q. Agents that are directly responsible bacterial killing after phagocytosis: (BSMMU - M. Phil, Diploma – July '10)**

- |                                   |  |
|-----------------------------------|--|
| a) Myeloperoxidase (MPO)          | T (MPO - Halide)                                   |
| b) Hypochlorite (HOCl)            | T  |
| c) Hydrogen peroxide ( $H_2O_2$ ) | T  |
| d) Lactoferrin                    | T (Ref: Robbins-9 <sup>th</sup> , P-81)            |
| e) Acid hydrolases                | F (Degrade the killed bacteria. Prof. Khaleque-27) |

**Q. Phagocytosis is promoted by:** (M. Phil, Diploma (DMC) - July-07)

- |                                   |   |
|-----------------------------------|---|
| a) complement components          | T |
| b) neuraminidase                  | F |
| c) hyaluronidase                  | F |
| d) the hexose monophosphate shunt | F |
| e) immunoglobulin                 | T |

**HELP LINK:**

The efficiency of phagocytosis is greatly enhanced when microbes are opsonized by specific proteins (opsonins) for which the phagocytes express high-affinity receptors. The major opsonins are IgG antibodies, the C3b breakdown product of complement, and certain plasma lectins, notably MBL, all of which are recognized by specific receptors on leukocytes.

**Q. Phagocytosis is facilitated by:** (DMC - M. Phil, Diploma, July.'06)

- |                                   |   |
|-----------------------------------|---|
| a) hyaluronidase                  | F |
| b) neuraminidase                  | F |
| c) the hexose monophosphate shunt | F |
| d) immunoglobulin                 | T |
| e) complement                     | T |

**Q. Bacterial killing can occur by oxygen independent mechanism through the action of –** (BSMMU - M. Phil, Diploma July-06)

- |  |  |
|--|--|
| a) Elastase                                      | T ( <i>neutrophil granules contain elastase that contribute to bacterial killing</i> ) |
| b) H <sub>2</sub> O <sub>2</sub>                 | F  |
| c) Lactoferrin                                   | T  |
| d) Lysozyme                                      | T  |
| e) H <sub>2</sub> O <sub>2</sub> -MPO-halide ion | F  |

**Q. Phagocytosis is a function of:** (MD/MS (DMC)-04Ja)

- |                 |   |
|-----------------|---|
| a) macrophages  | T |
| b) eosinophils  | F |
| c) basophils    | F |
| d) plasma cells | F |
| e) neutrophils  | T |

### Mononuclear phagocytic system

**Q. Mononuclear phagocytic system consists of** (BSMMU – Non-Residency – MD, MS, Basic science – July' 15)

- a) sinus histiocytes
- b) fibroblasts
- c) alveolar macrophages
- d) plasma cells
- e) kupffer cells

**Ans.**

a) True

b) False Fibroblasts are not related to the mononuclear phagocyte system although they may be found in close proximity to macrophages and epithelioid cells in granulomas. The function of fibroblasts is to secrete collagen.

c) True The macrophage is the prototype of the cells belonging to the mononuclear phagocyte system. One of the most important characteristics of this cell which was first described by Metchnikoff is its ability to phagocytose foreign particulate and colloidal particles, but they are also important in processing antigen for lymphocyte recognition. It is the active non-specific effector cell in cell-mediated immunity and in host resistance to infection by facultative and obligate intracellular microorganisms, e.g. mycobacteria, protozoa and viruses. Macrophages are derived from bone marrow precursors via circulating monocytes and they are easily recognised histologically by observing their uptake of carbon particles.

d) False

- e) **True** Kupffer cells are derived from precursor cells in the bone marrow that circulate as monocytes and then settle in the sinuses of the liver forming actively phagocytic cells.

### Leukocyte Induced Injury

**Q. Examples of chronic disorders caused by leukocyte induced injury are:** (BSMMU – MD/MS - 10Ja)

- |                       |   |
|-----------------------|---|
| a) arthritis          | T |
| b) asthma             | T |
| c) atherosclerosis    | T |
| d) glomerulonephritis | F |
| e) septic shock       | F |

**HELP LINK:**

Clinical Examples of Leukocyte-Induced Injury

Disorders	Cells and Molecules Involved in Injury
<b>ACUTE</b>	
Acute respiratory distress syndrome	Neutrophils
Asthma	Eosinophils; IgE antibodies
Glomerulonephritis	Antibodies and complement, neutrophils, monocytes;
Septic shock	Cytokines
<b>CHRONIC</b>	
Arthritis	Lymphocytes, macrophages; antibodies?
Asthma	Eosinophils; IgE antibodies
Atherosclerosis	Macrophages; lymphocytes?
Pulmonary fibrosis	Macrophages; fibroblasts

(Ref: Robbins & Cotran-9<sup>th</sup>, P-71)

**Q. Defect in phagocytosis results in the following diseases** (BSMMU – MS – January, 2010)

- |                               |   |
|-------------------------------|---|
| a) leukemia                   | T |
| b) anemia                     | T |
| c) diabetes                   | T |
| d) Chediak-Higashi syndrome   | T |
| e) myeloperoxidase deficiency | F |

[Ref: Prof. Khaleque, P-31]

**HELP LINK:**

**Defects in leucocytes function:** These include the following:

- **Inherited defects in leukocyte adhesion.** We previously mentioned the genetic defects of integrins and selectin-ligands that cause leukocyte adhesion deficiencies types 1 and 2. The major clinical problem in both is recurrent bacterial infections.
- **Inherited defects in phagolysosome function.** One such disorder is *Chédiak-Higashi syndrome*, an autosomal recessive condition characterized by defective fusion of phagosomes and lysosomes in phagocytes (causing susceptibility to infections), and abnormalities in melanocytes (leading to albinism), cells of the nervous system (associated with nerve defects), and platelets (causing bleeding disorders). The main leukocyte abnormalities are neutropenia (decreased numbers of neutrophils), defective degranulation, and delayed microbial killing. Leukocytes contain *giant granules*, which can be readily seen in peripheral blood smears and are thought to result from aberrant phagolysosome fusion. The gene associated with this disorder encodes a large cytosolic protein called LYST, which is believed to regulate lysosomal trafficking.
- **Inherited defects in microbicidal activity.** The importance of oxygen-dependent bactericidal mechanisms is shown by the existence of a group of congenital disorders called *chronic granulomatous disease*, which are characterized by defects in bacterial killing and render patients susceptible to recurrent bacterial infection.

Chronic granulomatous disease results from *inherited defects in the genes encoding components of phagocyte oxidase*, which generates O<sub>2</sub><sup>•</sup>. The most common variants are an X-linked defect in one of the membrane-bound components (gp91phox) and autosomal recessive defects in the genes encoding two of the cytoplasmic components (p47phox and p67phox). The name of this disease comes from the macrophage-rich chronic inflammatory reaction that tries to control the infection when the initial neutrophil defense is inadequate. This often leads to collections of activated macrophages that wall off the microbes, forming aggregates called *granulomas*.

**Acquired deficiencies.** Clinically, the most frequent cause of leukocyte defects is *bone marrow suppression*, leading to decreased production of leukocytes. This is seen following therapies for cancer (radiation and chemotherapy) and when the marrow space is compromised by tumors, which may arise in the marrow (e.g., leukemias) or be metastatic from other sites.

(Ref: Robbins & Cotran-8<sup>th</sup>, P-55)

#### Defects in Leukocyte Functions

Disease	Defect
<b>GENETIC</b>	
Leukocyte adhesion deficiency 1	Defective leukocyte adhesion because of mutations in β chain of CD11/CD18 integrins
Leukocyte adhesion deficiency 2	Defective leukocyte adhesion because of mutations in fucosyl transferase required for synthesis of sialylated oligosaccharide (ligand for selectins)
Chronic granulomatous disease X-linked	Decreased oxidative burst Phagocyte oxidase (membrane component)
Autosomal recessive	Phagocyte oxidase (cytoplasmic components)
MPO deficiency	Decreased microbial killing because of defective MPO—H <sub>2</sub> O <sub>2</sub> system
Chédiak-Higashi syndrome	Decreased leukocyte functions because of mutations affecting protein involved in lysosomal membrane traffic
<b>ACQUIRED</b>	
Bone marrow suppression: tumors, radiation, and chemotherapy	Production of leukocytes
Diabetes, malignancy, sepsis, chronic dialysis	Adhesion and chemotaxis
Leukemia, anemia, sepsis, diabetes, malnutrition	Phagocytosis and microbicidal activity

(Ref: Robbins & Cotran-8<sup>th</sup>, P-56)

Q Defect in leukocytes functions occur in (MD/MS (DMC) – 08Ja)

- a) Chronic granulomatous disease T
- b) Sarcoidosis F
- c) Hemodialysis T
- d) Chediak-Higashi syndrome T
- e) Lupus erythematosus F

Q Clinical examples of leukocyte induced injury are- (BSMMU-MD/MS-06Ja)

- A. Acute respiratory distress syndrome T
- B. Diabetes mellitus F
- C. Chronic granulomatous disease F
- D. Chronic transplant rejection T
- E. Idiopathic pulmonary fibrosis T

**Q. Defect in leukocytes functions occur in - (BSMMU-MD - 02Ja)**

- |                                  |   |
|----------------------------------|---|
| a) Chronic granulomatous disease | T |
| b) Sarcoidosis                   | F |
| c) Hemodialysis                  | T |
| d) Chediak-Higashi syndrome      | T |
| e) Lupus erythematosus           | F |

**INFLAMMATORY MEDIATORS****■ Chemical mediators:**

Mediator	Principal Sources	Actions
<b>CELL-DERIVED</b>		
Histamine	Mast cells, basophils, platelets	Vasodilation, increased vascular permeability, endothelial activation
Prostaglandins	Mast cells, leukocytes	Vasodilation, pain, fever
Leukotrienes	Mast cells, leukocytes	Increased vascular permeability, chemotaxis, leukocyte adhesion and activation
Cytokines (TNF, IL-1)	Macrophages, endothelial cells, mast cells	Local endothelial activation (expression of adhesion molecules), fever/pain/anorexia/hypotension, decreased vascular resistance (shock)
Chemokines	Leukocytes, activated macrophages	Chemotaxis, leukocyte activation
Platelet-activating factor	Leukocytes, mast cells	Vasodilation, increased vascular permeability, leukocyte adhesion, chemotaxis, degranulation, oxidative burst
<b>PLASMA PROTEIN DERIVED</b>		
Complement products (C5a, C3a, C4a)	Plasma (produced in liver)	Leukocyte chemotaxis and activation, direct target killing (membrane attack complex), vasodilation (mast cell stimulation)
Kinins	Plasma (produced in liver)	Increased vascular permeability, smooth muscle contraction, vasodilation, pain

(Ref: Robbins & Cotran-9<sup>th</sup>, P-83)**■ Functions of chemical mediators:**

Reaction of Inflammation	Principal Mediators
<b>Vasodilation</b>	Histamine, Serotonin, Bradykinin Prostaglandins, C3a, C4a, C5a, NO
<b>Increased vascular permeability</b>	Histamine, Serotonin, Bradykinin C3a and C5a (by liberating vasoactive amines from mast cells, other cells), C4a Leukotrienes C 4 , D 4 , E 4 PAF, PGD <sub>2</sub> , PGE <sub>2</sub> , Neuropeptide, Substance P
<b>Chemotaxis, leukocyte recruitment and activation</b>	TNF, IL-1 Chemokines C3a, C5a Leukotriene B 4
<b>Fever</b>	IL-1, TNF Prostaglandins
<b>Pain</b>	Prostaglandins Bradykinin
<b>Tissue damage</b>	Lysosomal enzymes of leukocytes Reactive oxygen species

(Ref: Robbins & Cotran-9<sup>th</sup>, P-90)

**Question Bank**

**Q. Chemical mediators of inflammation are (BSMMU – Residency - Dentistry – March' 19)**

- a) long lived
- b) important in stimulating the release of other mediators
- c) secreted by certain cells
- d) generated from plasma proteins
- e) overlapped in their actions

Ans. a) F (short lived) b) T c) T d) T e) T (Ref. Harsh Mohan-7<sup>th</sup>, P-122)

**Q. Chemicals sensitizing pain nerve ending are (BSMMU – Residency - MD/MS, Basic science, Paediatrics – March' 19)**

- a) serotonin
- b) substance P
- c) bradykinin
- d) encephalin
- e) prostaglandin E2

Ans. a) T b) T c) T d) F e) T

**Q. Capillary permeability is increased by (BSMMU – Residency - MD, MS, Basic Science, Dentistry - March' 17)**

- a) histamine
- b) vitamin C excess
- c) viral infection
- d) prolonged ischemia
- e) burn

Ans. a)T b)F c)T d)T e)T

**Help link:**

Reperfusion injury. Wikipedia  
damage caused when blood supply returns to the tissue after a period of ischemia or lack of oxygen (anoxia, hypoxia). The absence of oxygen and nutrients from blood during the ischemic period creates a condition in which the restoration of circulation results in inflammation and oxidative damage through the induction of oxidative stress rather than restoration of normal function.

**Mechanisms**

Reperfusion of ischemic tissues is often associated with microvascular injury, particularly due to increased permeability of capillaries and arterioles that lead to an increase of diffusion and fluid filtration across the tissues. Activated endothelial cells produce more reactive oxygen species but less nitric oxide following reperfusion, and the imbalance results in a subsequent inflammatory response.<sup>[1]</sup>

□ 2 ≡

**Q. Mediators that cause vasodilation are (BSMMU – Residency - MD, MS, Basic Science, Dentistry - March'**

**17)**

- a) prostaglandins
- b) bradykinin
- c) nitric oxide
- d) histamine
- e) C5a and C3a

Ans. a) T b) T c) T d)T e)T

**Q. In inflammation (BSMMU – Residency – MD, MS, Basic science, Dentistry – March' 16)**

- a) TNF is a chemokine with chemo-attractant properties
- b) TNF contributes to cachexia of disease
- c) TNF IL-1 are produced mainly by activated leukocytes
- d) histamine causes dilatation of arterioles
- e) one chemical mediator can stimulate the release of other mediators

Ans. a) F b) T c) F d) T e) T

**Q. The following chemical mediators are responsible for vasodilatation in acute inflammation (BSMMU – Residency - MD/MS, Basic science – March' 14)**

- |                   |   |
|-------------------|---|
| a) bradykinin     | T |
| b) histamin       | T |
| c) nitric oxide   | T |
| d) prostaglandins | T |
| e) leukotrienes.  | F |

**Q. Leukotrienes play a role in (BSMMU – Residency – MD, MS, Basic science, Dentistry – March' 16)**

- |                                    |   |
|------------------------------------|---|
| a) chemotaxis                      | T |
| b) vasoconstriction                | T |
| c) platelet aggregation            | F |
| d) bronchodilation                 | F |
| e) increased vascular permeability | T |

**Q. In acute inflammation, the chemical mediators have the following role (BSMMU –Residency – MD, MS, Basic – March' 15)**

- a) TNF causes direct tissue damage
- b) pain is produced by PAF
- c) histamine causes vasodilatation
- d) C<sub>3a</sub> is a chemotactic agent
- e) leukotriene have no effect on blood vessels

Ans. a) F b) F c) T d) F e) F

**Q. Vascular permeability of capillary is increased by (BSMMU – Non-Residency - MD – 13Ju)**

- |                               |   |
|-------------------------------|---|
| a) IL-6                       | F |
| b) IL-1                       | F |
| c) bradykinin                 | T |
| d) thromboxane A <sub>2</sub> | F |
| e) serotonin                  | T |

**O. The following mediators increase capillary permeability in acute inflammation: (BSMMU – M. Phil, Diploma (Non-Residency)–March-2012, DMC & others – MD/MS – March-2012)**

- |  |   |
|--|---|
| a) Histamine                             | T |
| b) Platelet Derived Growth Factor (PDGF) | F |
| c) Bradykinin                            | T |
| d) Angiotensin                           | F |
| e) Prostacyclin                          | F |

**Q. Preformed chemical mediators of inflammation are: (BSMMU – MD/MS (Residency) – January, 2011)**

- |                               |   |
|-------------------------------|---|
| a) histamine                  | T |
| b) prostaglandin              | F |
| c) lysosomal enzyme           | T |
| d) platelet activating factor | F |
| e) leukotriene                | F |

**Q. Vasodilation in inflammation is mediated by:** (BSMMU – MD – January, 2010)

- |                     |   |
|---------------------|---|
| a) histamine        | T |
| b) complement C5a   | T |
| c) leukotriene B4   | F |
| d) prostaglandin E1 | T |
| e) interleukin I    | F |

**Q. The following chemical mediators causes vasodilation in inflammation:** (BSMMU - M. Phil, Diploma – July '10)

- |   |   |
|---|---|
| a) Thromboxane A <sub>2</sub>                       | F |
| b) Prostacyclin (PGI <sub>2</sub> )                 | T |
| c) Prostaglandin D <sub>2</sub> (PGD <sub>2</sub> ) | T |
| d) Leukotriene C <sub>4</sub> (LTC <sub>4</sub> )   | F |
| e) LTE <sub>4</sub>                                 | F |

**Q. Prostaglandin is secreted from:** (BSMMU - M. Phil, Diploma, July-09)

- |                     |   |
|---------------------|---|
| a) all leukocytes   | T |
| b) macrophage       | T |
| c) platelet         | T |
| d) endothelial cell | T |
| e) eosinophil       | T |
- [Ref: Prof. Khaleque, P-31]
- [Ref: Prof. Khaleque]
- [Ref: Prof. Khaleque]

**Q. Preformed chemical mediators inflammation are:** (BSMMU – MD/MS - January, 2008)

- |                               |   |
|-------------------------------|---|
| a) Histamine                  | T |
| b) Prostaglandin              | F |
| c) Lysosomal enzyme           | T |
| d) Platelet activating factor | F |
| e) Nitric oxide               | F |

**Q. Inflammatory mediators include:** (MD/MS (DMC))-08Ja)

- |                                  |   |
|----------------------------------|---|
| a) Prostaglandin                 | T |
| b) Serotonin                     | T |
| c) anaphylotoxin                 | T |
| d) Membrane Attack Complex (MAC) | T |
| e) phospholipase A2              | F |

**Q. The mediators causes vasodilatation are:** (M. Phil, Diploma (BSMMU) - July-07)

- |                   |   |
|-------------------|---|
| a) Prostaglandins | T |
| b) Bradykinin     | T |
| c) Nitric oxide   | T |
| d) Histamine      | T |
| e) C3a and C5a    | T |

**Q. Preformed chemical mediators present within the cells are-** (BSMMU-MS-04Ja)

- |                      |   |
|----------------------|---|
| a) Cytokines         | F |
| b) Histamine         | T |
| c) Lysosomal enzymes | T |
| d) Nitric oxide      | F |
| e) Prostaglandins    | F |

**Q. Tissue damage in chronic inflammation is mediated by- (BSMMU-MS-04Ja)**

- |                                 |   |
|---------------------------------|---|
| a) Oxygen metabolites           | T |
| b) IL-1                         | F |
| c) Leukotriene C <sub>4</sub> . | F |
| d) Nitric oxide                 | T |
| e) Lysosomal enzymes            | T |

**Q. In inflammation, the following chemical mediator cause vasodilation (M. phil, Diploma (DMC) – 03Ju)**

- |                        |   |
|------------------------|---|
| a) Leukotriene D4      | F |
| b) Thromboxane A2      | F |
| c) (PGI2) prostacyclin | T |
| d) Histamine           | T |
| e) C3b                 | F |

**Q. Pain in inflammation is due to – (BSMMU-MD/MS - 02Ja)**

- |                       |   |
|-----------------------|---|
| a) Bacterial products | F |
| b) Prostaglandin      | T |
| c) Lysosomal enzymes  | F |
| d) Bradykinin         | T |
| e) C 5a               | F |

**Q. Chemical mediator in acute inflammation - (BSMMU-MS-01Ja)**

- |   |   |
|---|---|
| a) NO causes smooth muscle relaxation           | T |
| b) Bradykinin causes pain                       | T |
| c) C3b acts as anaphylatoxin                    | F |
| d) C5a is a chemokine                           | T |
| e) TXA <sub>2</sub> causes platelet aggregation | T |

## Nitric Oxide (NO)

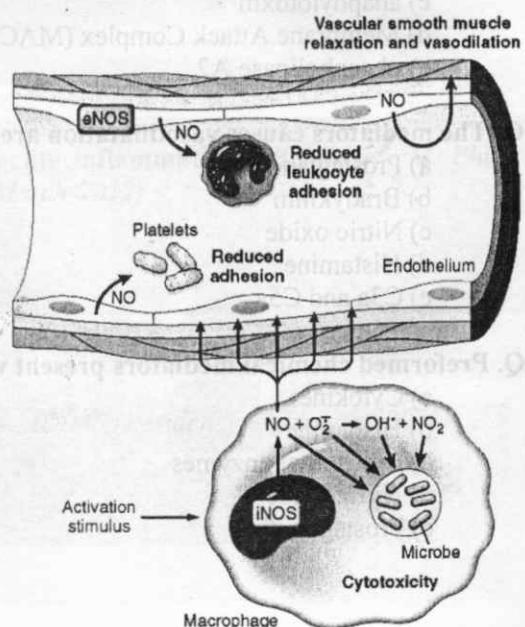
### NITRIC OXIDE (NO):

NO was discovered as a factor released from endothelial cells that caused vasodilation and was therefore called endothelium-derived relaxing factor. NO is a soluble gas that is produced not only by endothelial cells but also by macrophages and some neurons in the brain. It acts in a paracrine manner on target cells through induction of cyclic guanosine monophosphate, which, in turn, initiates a series of intracellular events leading to a response, such as the relaxation of vascular smooth muscle cells. Because the *in vivo* half-life of NO is only seconds, the gas acts only on cells in close proximity to where it is produced.

NO is synthesized from L-arginine by the enzyme nitric oxide synthase (NOS). There are three different types of NOS: endothelial (eNOS), neuronal (nNOS), and inducible (iNOS). eNOS and nNOS are constitutively expressed at low levels and can be activated rapidly by an increase in cytoplasmic Ca<sup>2+</sup>. iNOS, in contrast, is induced when macrophages and other cells are activated by cytokines (e.g., TNF, IFN-γ) or microbial products.

NO has dual actions in inflammation: it relaxes vascular smooth muscle and promotes vasodilation, thus contributing to the vascular reaction, but it is also an inhibitor of the cellular component of inflammatory responses.

NO reduces platelet aggregation and adhesion, inhibits several features of mast cell-induced inflammation, and inhibits leukocyte recruitment. Because of these inhibitory actions, production of NO is thought to be an endogenous mechanism for controlling inflammatory responses.



**FIGURE:** Functions of nitric oxide (NO) in blood vessels and macrophages. NO is produced by two NO synthase (NOS) enzymes. It causes vasodilation, and NO-derived free radicals are toxic to microbial and mammalian cells. *Now an inflammation has I-II in its foundations to inhibit a sudden emergency. NO and its derivatives are microbicidal, and thus NO is a mediator of host defense against infection. High levels of iNOS-induced NO are produced by leukocytes, mainly neutrophils and macrophages, in response to microbes.*

(Ref: Robbins & Cotran-8<sup>th</sup>, P-61)

**Q. Synthesis of nitric oxide requires (BSMMU – Non-Residency – MD, MS, Basic Science & Dentistry – July' 17)**

- a) NADPH
- b) ATP
- c) molecular oxygen
- d) nitric oxide synthase
- e) arginine

Ans. a) F b) F c) F d) T e) T

**Q. Nitric oxide (BSMMU – Residency - MD/MS, Basic science – March' 14)**

- a) is important for brain function
- b) is an autacoid
- c) reduces renal blood flow
- d) is concerned with receptive relaxation of the gut
- e) originates from arginine

Ans. a) T b) T c) F d) T e) T

**Q. Nitric oxide (NO) causes: (BSMMU – MD – January, 2010)**

- |  |   |
|--|---|
| a) vascular smooth muscle relaxation   | T |
| b) increased leukocyte adhesion        | F |
| c) increased platelet adhesion         | F |
| d) inhibition of bacterial replication | T |
| e) inhibition of tumour growth         | T |

[Ref: Prof. Khaleque]

**Q. Nitric oxide (BSMMU – MD/MS - January, 2009)**

- |   |   |
|---|---|
| a) is inhibited by the lipopolysaccharide of gram negative bacteria | F |
| b) is a neurotransmitter  | T |
| c) exists in a free-radical form which can be neurotoxic            | T |
| d) synthesis is stimulated by tumour necrosis factor                | T |
| e) is a useful therapy in angina                                    | T |

## Macrophage

**Q. Macrophages (BSMMU – Non-Residency – MD/MS, Basic science – July' 14)**

- a) have phagocytic but not pinocytic capabilities
- b) are derived from blood monocytes
- c) have a shorter life span than neutrophils
- d) contain neutral proteases
- e) produce interleukin -I

Ans. a) F b) T c) F d) T e) T

[Ref: Harsh mohan-7<sup>th</sup>, P-129]

### HELP LINK:

Macrophage:

Source:

1. Haematogenous from monocyte
2. Histogenous from liver (kupffer's) cells, lung (alveolar) macrophage, connective tissue (histocytes), spleen, lymph node and serous cavity.

### ■ Functions of macrophage:

1. Demolition.
2. Antimicrobial defense against intracellular invading organisms such as mycobacteria, leishmania and histoplasma.
3. Immunological function— macrophages are required to process and present antigen to immunocompetent T-cells.

4. Cellular immunity- Macrophages are important effector cells in certain form of cell mediated immunity e.g.- delayed hypersensitivity reaction.
5. Macrophages produce a variety of cytokines, such as IL-1 and TNF- $\alpha$ , are proinflammatory as well as fibrogenic.
6. They lyse tumour cell by secreting toxic metabolites and proteolytic enzyme and therefore may play a role in immunosurveillance.
7. Control of granulopoiesis and erythropoiesis— Macrophages control granulopoiesis by secreting colony stimulating factor and also control erythropoiesis by supplying ferritin for the synthesis of haemoglobin.

**Q. Macrophage is:** (BSMMU - M. Phil, Diploma-09Ju)

- |  |   |
|--|---|
| a) a component of mononuclear phagocyte system | T |
| b) the dominant cell in acute inflammation     | F |
| c) derived from monocyte                       | T |
| d) known as sinus histiocytes in lung          | F |
| e) known as Kupffer cells in liver             | T |

**Q. Macrophages-** (BSMMU-MD/MS- 02Ja)

- |  |   |
|--|---|
| a) Play central role in chronic inflammation | T |
| b) Are only activated by lymphokines         | F |
| c) Have myeloperoxidase enzyme               | F |
| d) Can release angiogenesis factor           | T |
| e) Are motile.                               | F |

### Tumour necrosis factor (TNF)

**Q. TNF $\alpha$  (tumour necrosis factor alpha) (BSMMU – Residency - Dentistry - March' 17)**

- a) is produced by T-lymphocytes
- b) acts on the hypothalamus to produce fever
- c) has an antiviral effect
- d) causes hypertension
- e) causes hypercoagubility

Ans. a) T b) T c) Td)F e)T

**Help Link:**

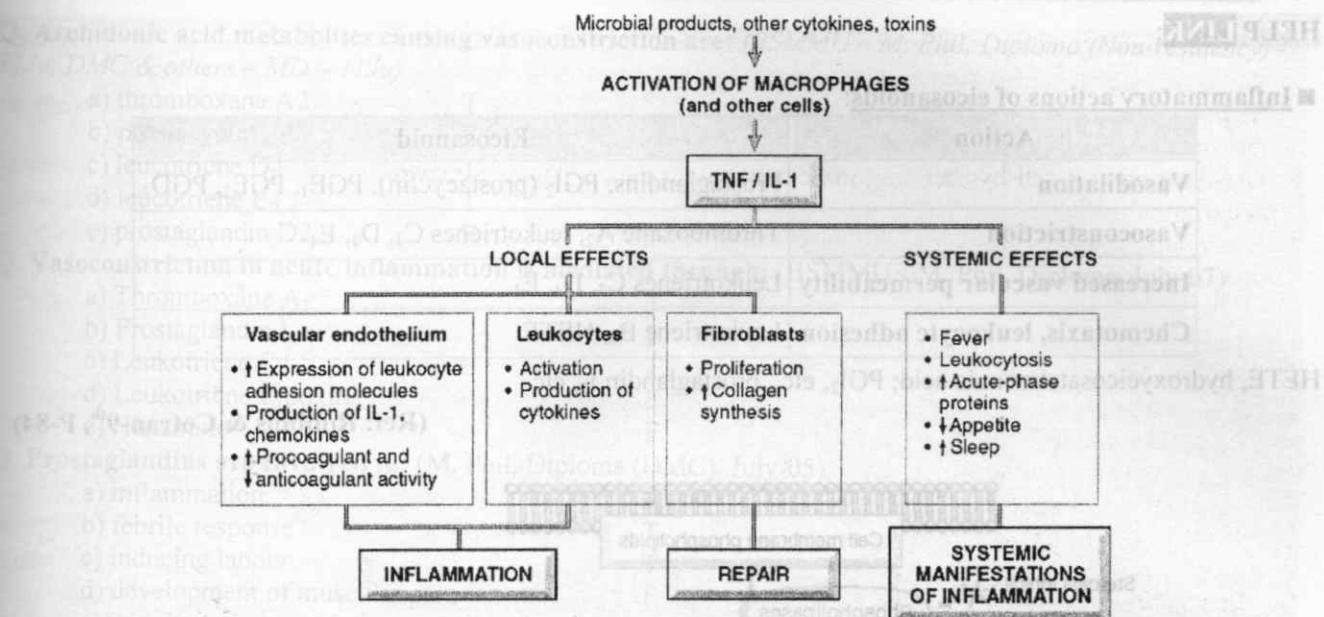
**TNF (tumour necrosis factor)**

- TNF is a cytokine.
- Cytokines are proteins
- TNF are produced mainly by activated macrophages & T lymphocytes
- In high conc it causes activation of coagulation system

**Source:** Activated macrophage.

NO has dual actions in inflammation: it relaxes vascular smooth muscle and promotes vasoconstriction, thus contributing to the vascular resistance. It may also inhibit the cellular movement of inflammatory responses.

NO reduces platelet aggregation and adhesion, inhibits several features of mast cell-induced inflammation, and inhibits leukocyte infiltration. Similarily, nitric oxide is thought to inhibit angiogenesis, which is thought to be an endogenous mechanism for controlling angiogenesis during the process of wound healing.



**FIG:** Principal local and systemic actions of tumor necrosis factor (TNF) and interleukin-1 (IL-1).  
(Ref: Robbins & Cotran-8<sup>th</sup>, P-62)

**Secretion stimulated by:**

- ✓ Endotoxin and other microbial products
- ✓ Immune complex
- ✓ Physical injury
- ✓ Various inflammatory stimuli.

**Function:**

1. In endothelium:
  - Endothelial activation
  - Expression of endothelial adhesion molecule
  - Synthesis of chemical mediator: Cytokines, chemokines, growth factor, eicosanoids, NO.
2. Production of enzymes associated with matrix remodeling.
3. Increased in the surface thrombogenicity of the endothelium.

**Q. Tumour necrosis factor (TNF) - (MD/MS (DMC)-09Ja)**

- a. is found in plasma
- b. is a protein
- c. is beneficial to host
- d. inhibits mitochondrial respiration
- e. has anti-viral activity

- F
  - T
  - T
  - F
  - T
- (Ref: Prof. Akram Immunology 5<sup>th</sup> edition, P-113)

## ARACHIDONIC ACID METABOLITES

**Q. Regarding eicosanoids (BSMMU-Residency - MD, MS, Basic - March '15)**

- a) these are derivatives of twenty carbon saturated fatty acids
- b) leukotriens are product of cyclooxygenase pathway
- c) prostaglandin I<sub>2</sub> inhibits platelet aggregation
- d) TXA<sub>1</sub> is more potent than TXA<sub>2</sub>
- e) leukotriens are chemoattractant

Ans. a) F b) F c) T  
d) F (TXA<sub>2</sub> is more potent because it causes aggregation of platelets leads to thrombus formation)

[Ref: ABC Biochemistry]

- e) T

**HELP LINK:****■ Inflammatory actions of eicosanoids:**

Action	Eicosanoid
Vasodilation	Prostaglandins, PGI <sub>2</sub> (prostacyclin), PGE <sub>1</sub> , PGE <sub>2</sub> , PGD <sub>2</sub>
Vasoconstriction	Thromboxane A <sub>2</sub> , leukotrienes C <sub>4</sub> , D <sub>4</sub> , E <sub>4</sub>
Increased vascular permeability	Leukotrienes C <sub>4</sub> , D <sub>4</sub> , E <sub>4</sub>
Chemotaxis, leukocyte adhesion	Leukotriene B <sub>4</sub> , HETE

HETE, hydroxyeicosatetraenoic acid; PGI<sub>2</sub>, etc., prostaglandin I<sub>2</sub>, etc.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-84)

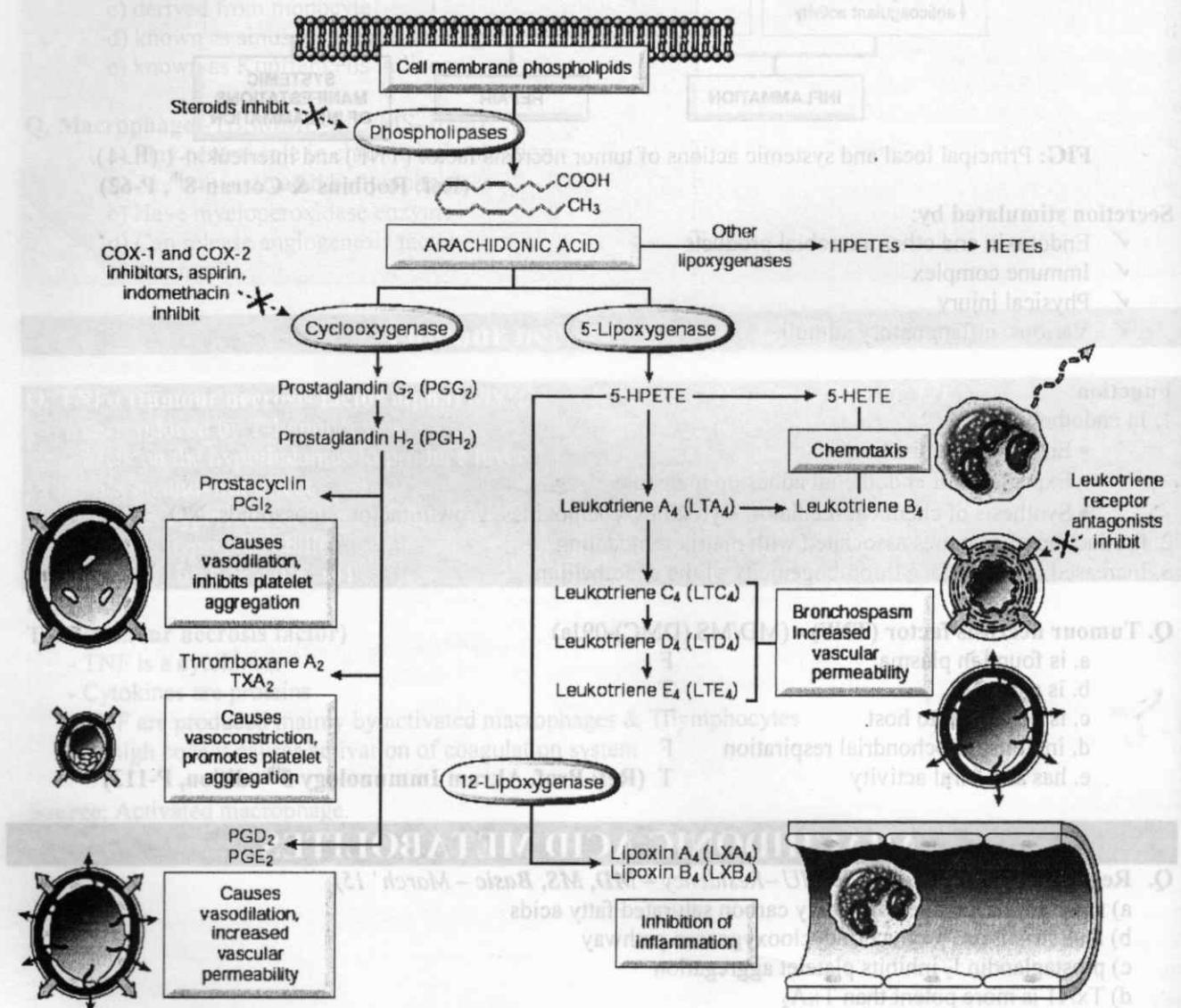


Fig. Generation of arachidonic acid metabolites and their roles in inflammation. The molecular targets of action of some anti-inflammatory drugs are indicated by a black x. COX, cyclooxygenase; HETE, hydroxyeicosatetraenoic acid; HPETE, hydroperoxyeicosatetraenoic acid.

**Q. Arachidonic acid metabolites causing vasoconstriction are: (BSMMU – M. Phil, Diploma (Non-residency) – IIJu, DMC & others – MD – IJu)**

- |                                 |   |
|---------------------------------|---|
| a) thromboxane A <sub>2</sub>   | T |
| b) prostacyclin                 | F |
| c) leucotriene D <sub>4</sub>   | T |
| d) leucotriene E <sub>4</sub>   | T |
| e) prostaglandin D <sub>2</sub> | F |

**Q. Vasoconstriction in acute inflammation is mediated through: (BSMMU - M. Phil, Diploma, July-07)**

- |                                 |   |
|---------------------------------|---|
| a) Thromboxane A <sub>2</sub>   | T |
| b) Prostaglandin I <sub>2</sub> | F |
| c) Leukotriene C <sub>4</sub>   | T |
| d) Leukotriene Lipoxins         | F |
| e) Histamine                    | F |

**Q. Prostaglandins are Involved in: (M. Phil, Diploma (DMC), July-05)**

- |  |   |
|--|---|
| a) inflammation                            | T |
| b) febrile response                        | T |
| c) inducing labour                         | T |
| d) development of muscular pain            | F |
| e) with bronchoconstriction and dilatation | F |

**Q. The following arachidonic acid metabolites are vasodialator - (M. Phil, Diploma (BSMMU) - July-04)**

- |   |   |
|---|---|
| A. Leukotrine B <sub>4</sub>                        | F |
| B. Prostaglandins E <sub>1</sub> and E <sub>2</sub> | T |
| C. Thromboxane A <sub>2</sub>                       | F |
| D. Endoperoxide                                     | F |
| E. Prostaglandin I <sub>2</sub>                     | T |

**Q. The arachidonic acid metabolites of the cyclooxygenase pathway are: [MD/MS (DMC) - 04Ja]**

- |                     |   |
|---------------------|---|
| a. PGE <sub>2</sub> | T |
| b. PGD <sub>2</sub> | T |
| c. PGI <sub>2</sub> | T |
| d. TXA <sub>2</sub> | T |
| e. Lipoxin          | F |

## Systemic Effects of Inflammation

**Q. Systemic effects of inflammation are (BSMMU – Non-Residency – Dentistry – July' 19)**

- a) increased heart rate
- b) cold clammy skin
- c) fever
- d) leukocytosis
- e) hypotension

Ans. a) T   b) F   c) T   d) T   e) F

**Help Link:**

The systemic changes associated with acute inflammation are collectively called the *acute-phase response*, or the systemic inflammatory response syndrome (SIRS).

**I. Fever:** characterized by an elevation of body temperature, usually by 1° to 4°C. Fever is produced in response to substances called *pyrogens* that act by stimulating prostaglandin synthesis. Bacterial products, such as LPS (called *exogenous pyrogens*), stimulate leukocytes to release cytokines such as IL-1 and TNF (called *endogenous pyrogens*).

2. **Acute-phase proteins:** These are the plasma proteins, mostly synthesized in the liver, whose plasma concentrations may increase several hundred-fold as part of the response to inflammatory stimuli. Three of the best-known of these proteins are C-reactive protein (CRP), fibrinogen, and serum amyloid A (SAA) protein.
3. **Leukocytosis:** It is a common feature of inflammatory reactions, especially those induced by bacterial infections. The leukocyte count usually climbs to 15,000 or 20,000 cells/ $\mu\text{L}$ , but sometimes it may reach extraordinarily high levels of 40,000 to 100,000 cells/ $\mu\text{L}$ . These extreme elevations are referred to as **leukemoid reactions**.
4. Other manifestations of the acute-phase response include
  - increased pulse and blood pressure;
  - decreased sweating, mainly because of redirection of blood flow from cutaneous to deep vascular beds, to minimize heat loss through the skin;
  - rigors (shivering), chills (search for warmth), anorexia, somnolence, and malaise, probably because of the actions of cytokines on brain cells.
5. **Sepsis:** In severe bacterial infections (sepsis), the large amounts of bacteria and their products in the blood stimulate the production of enormous quantities of several cytokines, notably TNF and IL-1. High blood levels of cytokines cause various widespread clinical manifestations such as disseminated intravascular coagulation, hypotensive shock, and metabolic disturbances including insulin resistance and hyperglycemia. This clinical triad is known as septic shock.

(Ref: Robbins & Cotran – 9<sup>th</sup>, P-99-100)

## Acute phase reactions

**Q. Acute phase proteins are (BSMMU – Residency - Dentistry – March' 19)**

- a) C-reactive protein
- b) fibrinogen
- c) mannose binding protein
- d) antibody
- e) prostaglandin

Ans. a) T b) T c) T d) F e) F

**Q. Acute phase response is characterized by (BSMMU – Non-Residency – MD, MS, Basic science – July' 18)**

- a) generation of IL-1
- b) increased concentration of serum amyloid A
- c) thrombocytopenia
- d) decreased rouleaux formation
- e) lymphocytosis

Ans. a) T b) T c) T (Ref: Klaleque sir, page 42) d) F (increased) e) T (also neutrophilia and eosinophilia)

(Ref: Robbin's-9<sup>th</sup>, P-99)

**Q. Acute phase proteins are (BSMMU – Diploma - Dentistry – July' 18)**

- a) fibrinogen
- b) mannan binding protein
- c) serum amyloids
- d) prothrombin
- e) chondroitin sulphate

Ans. a) T b) T c) T d) F e) F

**HELP LINK:**

**Acute-phase proteins** are plasma proteins, mostly synthesized in the liver, whose plasma concentrations may increase several hundred-fold as part of response to inflammatory stimuli. Three of the best-known examples of these proteins are C-reactive protein (CRP), fibrinogen, and serum amyloid A protein (SAA).

#### Examples:

- C-reactive protein
- Haptoglobin
- Amyloid A (serum)
- $\alpha_1$  antitrypsin
- $\alpha_1$  antichymotrypsin
- Transferrin & ferritin
- Fibrinogen
- Lactoferrin
- Manganese superoxide dismutase

Synthesis of these molecules by hepatocytes is upregulated by cytokines, especially IL-6 (for CRP and fibrinogen) and IL-1 or TNF (for SAA). Many acute-phase proteins, such as CRP and SAA, bind to microbial cell walls, and they may act as opsonins and fix complement.

C-reactive protein is an acute phase reactant which opsonises invading pathogens. Levels of CRP increase within 6 hours of an inflammatory stimulus, and may rise up to 1000-fold. Measurement of CRP provides a **direct Index** of acute inflammation, and fibrinogen, and serum amyloid A protein the plasma half-life of CRP is 19 hours, so levels fall in just a few days once the stimulus is removed. Sequential measurement is useful in monitoring disease activity. For reasons which remain unclear, some diseases are associated with only minor elevations of CRP concentration despite unequivocal evidence of active inflammation. These include SLE, scleroderma, ulcerative colitis and leukaemia. Importantly, intercurrent infection does provoke a significant CRP response in these conditions.

#### Regarding function of acute phase proteins:

- C-reactive protein & serum amyloid A contribute to the host defense & stimulate repair & regeneration
- Fibrinogen plays an essential role in wound healing
- $\alpha_1$ -antitrypsin &  $\alpha_1$  antichymotrypsin control the pro-inflammatory cascade by neutralizing the enzymes produced by activated neutrophils, preventing wide-spread tissue destruction
- Haptoglobin & manganese superoxide dismutase scavenge for oxygen free radicals
- Transferrin, ferritin and lactoferrin decrease the iron available for uptake by bacteria

**Q. Acute phase proteins are (BSMMU – Residency - MD, MS, Basic Science - March' 17)**

- a) fibrinogen
  - b) haemoglobin
  - c) heptoglobin
  - d) prothrombin
  - e) serum amyloid protein
- Ans. a) T b) F c) T d) F e) T**

**Q. Features of systemic inflammatory response syndrome are (BSMMU – Residency – MD, Dentistry – March' 16)**

- |   |   |
|---|---|
| a) temperature $> 38.0^{\circ}\text{C}$         | T |
| b) respiratory rate $> 20/\text{min}$           | T |
| c) heart rate $> 90/\text{minutes}$             | T |
| d) white cell count $> 12 \times 10^9/\text{L}$ | T |
| e) blood glucose $< 3 \text{ mmol/L}$           | F |
- (Ref: Robbins-9<sup>th</sup>, P-99)

**Q. Acute phase reaction include: (BSMMU – M. Phil, Diploma (Non-Residency)–March-2012, DMC & others – MD/MS – March-2012**

- |                                       |   |
|---------------------------------------|---|
| a) increased sleep                    | T |
| b) decreased CRP (c reactive protein) | F |
| c) increased ESR                      | T |
| d) increased appetite                 | F |
| e) fever                              | T |

**Q. Acute phase reaction includes: (BSMMU – MD/MS (Residency) – January, 2011)**

- |                       |   |
|-----------------------|---|
| a) fever              | T |
| b) increased appetite | F |
| c) increases sleep    | T |
| d) decreased CRP      | F |
| e) increased ESR      | T |

**Q. Acute phase reactions are: (BSMMU – MD/MS - January, 2008)**

- |                                  |   |
|----------------------------------|---|
| a) fever                         | T |
| b) insomnia                      | F |
| c) loss of appetite              | T |
| d) increased acute phase protein | T |
| e) neutropenia                   | F |

### C-reactive protein (CRP)

**Q. C-reactive protein (CRP) (BSMMU – Residency – MS – March '18)**

- a) does not have antigen specificity
- b) increases significantly in acute viral infections
- c) is produced in the liver
- d) is a useful investigation in the management of bacterial endocarditis
- e) activates complement system by the classical pathway

Ans. a) T b) T (Ref: Davidson) c) T d) T e) T

**Q. C-reactive protein (CRP): (BSMMU – Residency – MD/MS – March '15/ 13)**

- a) Does not have antigen specificity
- b) Levels increase significantly in acute viral infections
- c) Is produced in the liver
- d) Measurement is useful in the management of bacterial endocarditis
- e) Activates complement by the classical pathway

Ans : a) T b) T c) T d) T e) T

**Help link:**

**সূত্র: C-reactive protein increases in: ‘CAMBRIAN’**

C = Connective tissue disorders (except SLE)

A = Acute infection due to bacteria, virus & fungus

M = Malignancy

B = Bacterial necrotizing infection

R = Rheumatça (poymyalgia rheumatica)

I = Introduction of steroids

A = Acute inflammatory diseases eg. Crohn's diseases, systemic vasculitides, giant cell arteritis

N = Necrosis of myocardium eg. Acute MI

**সূত্র: C-reactive protein is not raised in: PALU’S HOME (পালুর ঘর)**

L = Leukaemia

U = Ulcerative colitis

P = Pregnancy

Polycythaemia

A = Anaemia (macrocytic anaemia)

S = SLE

Sjogrens syndrome

H = Heart failure

O = Old age

M = Myeloma

E = End stage renal disease

**Q. C-reactive protein (CRP) (BSMMU – MD/MS (Residency) – January, 2011)**

- |  |   |
|--|---|
| a) measurement is an indirect index of acute inflammation                      | F |
| b) is a late indicator of acute inflammation                                   | F |
| c) is synthesized in the liver   | T |
| d) synthesis is upregulated by TNF   | T |
| e) Concentration in plasma increase several hundred fold in acute inflammation | T |

## GRANULOMATOUS INFLAMMATION

**Granulomatous inflammation:**

Granulomatous inflammation is a form of chronic inflammation characterized by collections of activated macrophages, often with T lymphocytes, and sometimes associated with central necrosis.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-97)

**Classification & Example:**

1. **Bacterial:** Tuberculosis, leprosy, syphilis, cat-scratch disease, brucellosis, lymphogranuloma inguinale.
2. **Fungal:** Rhinosporidiosis, histoplasmosis, cryptococcosis.
3. **Parasitic:** Schistosomiasis.
4. **Inorganic metals:** Berylliosis.
5. **Unknown:** Sarcoidosis

**Examples of Diseases with Granulomatous Inflammation:**

Disease	Cause	Tissue Reaction
Tuberculosis	<i>Mycobacterium tuberculosis</i>	Caseating granuloma (tubercle): focus of activated macrophages (epithelioid cells), rimmed by fibroblasts, lymphocytes, histiocytes, occasional Langhans giant cells; central necrosis with amorphous granular debris; acid-fast bacilli
Leprosy	<i>Mycobacterium leprae</i>	Acid-fast bacilli in macrophages; noncaseating granulomas
Syphilis	<i>Treponema pallidum</i>	Gumma: microscopic to grossly visible lesion, enclosing wall of histiocytes; plasma cell infiltrate; central cells necrotic without loss of cellular outline
Cat-scratch disease	Gram-negative bacillus	Rounded or stellate granuloma containing central granular debris and recognizable neutrophils; giant cells uncommon
Sarcoidosis	Unknown etiology	Noncaseating granulomas with abundant activated macrophages
Crohn disease (inflammatory bowel disease)	Immune reaction against intestinal bacteria, self-antigens	Occasional noncaseating granulomas in the wall of the intestine, with dense chronic inflammatory infiltrate

**Granuloma:****Definition:**

Granuloma formation is a cellular attempt to contain an offending agent that is difficult to eradicate. In this attempt there is often strong activation of T lymphocytes leading to macrophage activation, which can cause injury to normal tissues. The activated macrophages may develop abundant cytoplasm and begin to resemble epithelial cells, and are called epithelioid cells. Some activated macrophages may fuse, forming multinucleate giant cells.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-97)

**Causes of granuloma formation:**

1. Foreign body granuloma: Talc, sutures or other fibres.
2. Immune granuloma:
  - a. *Mycobacterium tuberculosis*
  - b. *Mycobacterium leprae*
  - c. *Treponema pallidum*
  - d. Gram – negative bacillus (cat-scratch disease).

(Ref: Robbins & Cotran-9<sup>th</sup>, P-97)

**Examples of non-caseating granuloma:**

1. Hard tubercle of tuberculosis
2. Tuberculoid leprosy
3. Sarciodosis
4. Foreign body granuloma
5. Schistosomiasis

**Example of suppurative granulomatous inflammation:**

1. Lymphogranuloma venereum
2. Cat scratch disease

**Classification:** 2 types.

There are two types of granulomas, which differ in their pathogenesis.

• **Foreign body granulomas** are incited by relatively inert foreign bodies, in the absence of T cell-mediated immune responses. Typically, foreign body granulomas form around materials such as talc (associated with intravenous drug abuse) (Chapter 9), sutures, or other fibers that are large enough to preclude phagocytosis by a macrophage and do not incite any specific inflammatory or immune response. Epithelioid cells and giant cells are apposed to the surface of the foreign body. The foreign material can usually be identified in the center of the granuloma, particularly if viewed with polarized light, in which it appears refractile.

• **Immune granulomas** are caused by a variety of agents that are capable of inducing a persistent T cell-mediated immune response. This type of immune response produces granulomas usually when the inciting agent is difficult to eradicate, such as a persistent microbe or a self antigen. In such responses, macrophages activate T cells to produce cytokines, such as IL-2, which activates other T cells, perpetuating the response, and IFN- $\gamma$ , which activates the macrophages. It is not established which macrophage-activating cytokines (IL-4 or IFN- $\gamma$ ) transform the cells into epithelioid cells and multinucleate giant cells.

**MORPHOLOGY:** In the usual hematoxylin and eosin preparations, the activated macrophages in granulomas have pink granular cytoplasm with indistinct cell boundaries and are called epithelioid cells because of their resemblance to epithelia. The aggregates of epithelioid macrophages are surrounded by a collar of lymphocytes. Older granulomas may have a rim of fibroblasts and connective tissue. Frequently, but not invariably, multinucleated giant cells 40 to 50  $\mu\text{m}$  in diameter are found in granulomas; these are called Langhans giant cells. They consist of a large mass of cytoplasm and many nuclei, and they derive from the fusion of multiple activated macrophages. In granulomas associated with certain infectious organisms (most classically *Mycobacterium tuberculosis*), a combination of hypoxia and free radical-

mediated injury leads to a central zone of necrosis. Grossly, this has a granular, cheesy appearance and is therefore called caseous necrosis. Microscopically, this necrotic material appears as amorphous, structureless, eosinophilic, granular debris, with complete loss of cellular details. The granulomas in Crohn disease, sarcoidosis, and foreign body reactions tend to not have necrotic centers and are said to be noncaseating. Healing of granulomas is accompanied by fibrosis that may be extensive.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-97-98)

**Q. Examples of granulomatous inflammation are (BSMMU – Non-Residency – Dentistry – July' 19)**

- a) sarcoidosis
- b) lupus vulgaris
- c) tuberculosis
- d) psoriasis
- e) candidiasis

Ans. a) T b) T (granuloma rae produced with no necrosis, its a skin TB) c) T d) F e) F (Rarely produce granuloma)

**Q. Granuloma formation is/are frequently associated with (BSMMU – Residency - MD/MS, Basic science, Paediatrics, Dentistry – March' 19)**

- a) healing process
- b) acute inflammation
- c) wound contracture
- d) angiogenesis
- e) persistent irritants

Ans. a) F b) F c) F d) F e) T (Foreign body granuloma formation is seen by persistent or chronic irritation)

**Q. Granulomatous inflammation is found in (BSMMU – Diploma - Dentistry – July' 18)**

- a) syphilis
- b) gonorrhea
- c) Crohn's disease
- d) ulcerative colitis
- e) sarcoidosis

Ans. a) T b) F c) T d) F e) T

(Ref: Robbin's 9<sup>th</sup>, P-98)

**Q. Granuloma are found in (BSMMU – Residency - MD, MS, Basic Science, Dentistry - March' 17)**

- a) leprosy
- b) syphilis
- c) brucellosis
- d) rickettsia
- e) cryptococcosis

Ans. a) T b) T c) T d) F e) T

**Q. Granulomatous inflammatory diseases are (BSMMU – Residency - Dentistry - March' 17)**

- a) candidiasis
- b) aspergillosis
- c) pneumoconiosis
- d) sarcoidosis
- e) giardiasis

Ans. a) F(rarely formed granuloma) b) T c) T d) T e) F

**Q. Granulomas are composed of (BSMMU – Residency - MD, MS, Basic science, Dentistry – March' 16)**

- |                                 |                                 |
|---------------------------------|---------------------------------|
| a) epithelioid cells            | T                               |
| b) lymphocytes                  | T                               |
| c) newly formed blood vessels   | F (found in granulation tissue) |
| d) Langhans type of giant cells | T                               |
| e) granulation tissue           | F                               |

**Q. Granulomatous inflammation (BSMMU – Non-Residency – MD, MS, Basic science – July' 15)**

- |   |   |
|---|---|
| a) is a type III hypersensitivity response                    | F |
| b) shows dominant infiltration of tissue by plasma cells      | F |
| c) contains epithelioid cells derived from tissue histiocytes | T |
| d) occurs in sarcoidosis                                      | T |
| e) occurs in visceral leishmaniasis                           | F |

**Help link:** Cutaneous & mucocutaneous lesion – granulomatous lesion. [Ref: Robbins-9<sup>th</sup>, P-393]

**Q. Granulomatous lesions are produced by (BSMMU – Non-Residency – MD/MS, Basic science – July' 14)**

- a) *Mycobacterium tuberculosis*
- b) *Brucella abortus*
- c) *Shigella flexneri*
- d) *Candida albicans*
- e) *Histoplasma capsulatum*

Ans. a) T b) T c) F d) F (occasionally Robbin's Path-9<sup>th</sup>, P-387) e) T

**Question Bank****Q. Epithelioid cell granuloma is found in (BSMMU – Residency – MD, MS, Basic Science – March' 18)**

- a) syphilis
- b) rhinosporodiosis
- c) amyloidosis
- d) sarcoidosis
- e) toxoplasmosis

Ans. a) T b) T c) F d) T e) T

**Q. Granulomatous diseases are (BSMMU – Residency – MD, MS, Basic – March' 15)**

- a) pneumoconiosis
- b) candidiasis
- c) aspergillosis
- d) sarcidosis
- e) cat scratch disease

Ans. a) T b) F (occasionally granuloma forms Robbin's Path-9<sup>th</sup>, P-387) c) T d) T e) T

**Q. Langhan's giant cells (BSMMU – Non-Residency – MD/MS, Basic science – July' 14)**

- a) have a peripheral ring of nuclei with central clearing
- b) are the antigen presenting cells in the skin
- c) have nuclei scattered randomly through the cytoplasm
- d) are characteristically seen in tuberculosis
- e) are derived from macrophages

Ans. a) T b) F c) F d) T e) T

**Help link:** Langerhans cell - skin

**Q. The following organisms characteristically induce a granulomatous inflammatory response (BSMMU – Residency - MD/MS, Basic science – March' 14)**

- |                                      |   |
|--------------------------------------|---|
| a) <i>mycobacterium tuberculosis</i> | T |
| b) <i>staphylococcus aureus</i>      | F |
| c) <i>treponema pallidum</i>         | T |
| d) <i>mycobacterium leprae</i>       | T |
| e) <i>streptococcus pneumoniae</i>   | F |

**Q. A non caseating granuloma:** (BSMMU – Residency – MD/MS – March'13)

- a) Is not a feature of tuberculosis
- b) Can be seen in tuberculoid leprosy
- c) Is always found in Sarcoidosis
- d) Is a typical feature of syphilis
- e) Is found in foreign body reaction

**Ans:** a) T b) T c) T d) T e) T

**Q. Examples of diseases with granulomatous inflammation are:** (BSMMU – M. Phil, Diploma (Non-Residency) – March-2012, DMC & others – MD/MS – March-2012)

- |                        |   |
|------------------------|---|
| a) Sarcoidosis         | T |
| b) Crohn disease       | T |
| c) Cat scratch disease | T |
| d) Ochronosis          | F |
| e) Parkinson disease   | F |

**Q. Granulomas in tuberculosis:** (BSMMU – MD/MS (Residency) – January, 2011)

- |  |   |
|--|---|
| a) are discrete in nature              | T |
| b) always contain giant cells          | F |
| c) may show central caseation necrosis | T |
| d) heal by fibrosis                    | T |
| e) are made of epithelioid cells.      | T |

**Q. Cell types found in an established granuloma include:** (BSMMU-M Phil, Diploma, July-09)

- |                            |   |
|----------------------------|---|
| a) Histiocytes             | F |
| b) Neutrophils             | F |
| c) Activated T lymphocytes | T |
| d) Langerhans giant cells  | F |
| e) Epithelioid cells       | T |

**Q. Examples of diseases with Granulomatous inflammation are:** (BSMMU - M. Phil, Diploma July-07)

- |                                  |   |
|----------------------------------|---|
| a) Sarcoidosis                   | T |
| b) Tuberculosis                  | T |
| c) Pyogenic granuloma            | F |
| c) Crohn's disease               | T |
| e) Chronic granulomatous disease | T |

**Q. In tubercular lesions -** (BSMMU - M. Phil, Diploma, July-06)

- |   |   |
|---|---|
| a) There is accumulation of epithelioid cells     | T |
| b) Caseation necrosis is always present           | F |
| c) Lymphocytes are plenty compared to sarcoidosis | T |
| d) Mycobacteria are always demonstrable           | F |
| e) Healing may be followed by calcification.      | T |

**Q. Granulomatous inflammation seen in:** (M. Phil, Diploma (DMC) - July-05)

- |                 |   |
|-----------------|---|
| a) Tuberculosis | T |
| b) Lymphoma     | F |
| c) Antiboma     | F |
| d) Sarcoidosis  | T |
| e) Syphilis     | T |

**Q. Granuloma is (M. Phil, Diploma (BSMMU) - July-05)**

- |   |                                  |
|---|----------------------------------|
| A. composed of epitheloid cells                                     | T                                |
| B. soft pink granular in naked eye                                  | F (This is a granulation tissue) |
| C. composed of newly formed capillaries & proliferating fibroblasts | F                                |
| D. a highly vascularized connective tissue                          | F                                |
| E. a tissue reaction due to Type IV hypersensitivity                | T                                |

**Q. Granulomas are found in following diseases: (M. phil, Diploma (DMC) – 03Ju)**

- |                      |   |
|----------------------|---|
| a. Tuberculosis      | T |
| b. Chorn's disease   | T |
| c. Mycosis fungoides | F |
| d. Cellulites        | F |
| e. Leishmaniasis     | F |

**Help link:**

1. Cutaneous leishmaniasis causes granulomatous inflammation.
2. Muco-cutaneous leishmaniasis causes granulomatous inflammation.
3. Visceral leishmaniasis causes no granulomatous inflammation.

In BD, Visceral leishmaniasis is common. For that reason the answer is False. [Ref: Robbins-9<sup>th</sup>, P-393]

**GIANT CELLS****Q. Giant cells may be seen – (MD/MS (DMC) – 08Ja)**

- |                       |   |
|-----------------------|---|
| a) fibroxanthoma      | T |
| b) ulcerative colitis | F |
| c) measles            | T |
| d) chicken pox        | F |
| e) crohn's disease    | F |

**HELP LINK:**

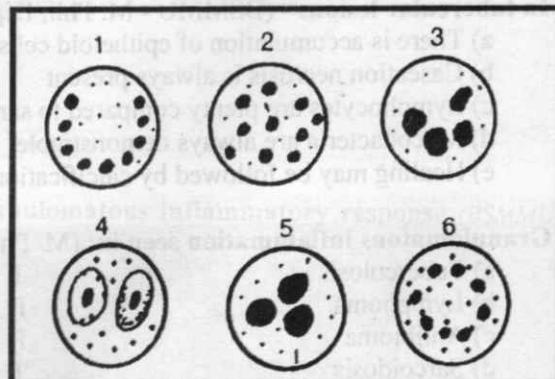
Giant cells are large cells with more than one nucleus. They are also called multinucleated cells. Size and number of nuclei varies.

**■ Types of giant cells:****A. Physiological giant cells:**

Osteoclasts, megakaryocytes and syncytiotrophoblast of the placenta.

**B. Pathological giant cells:****I. Giant cells formed by fusion of monocytes/ macrophages:**

1. Langerhan's giant cell of granulomatous inflammation, e.g. in tubercle of tuberculosis.
2. Foreign body giant cell of granulomatous inflammation, e.g. in reaction due to talc silica.
3. Aschoff giant cell in rheumatic lesions formed by fusion of histiocytes (macrophages)
4. Giant cells of giant cell tumour of bone. It is believed to form via fusion of monocytes/ macrophages. These are osteoclast-type giant cells.
5. Tuoton giant cell in xanthomata.
6. Giant cells to reaction to sodium urate crystal in gout.



**Fig: 1. Langerhan's giant cell 2. Foreign body giant cell 3. Malignant giant cell 4. Reed-sternberg giant cell 5. Aschoff giant cell 6. Tuoton giant cell**

**Malignant giant cells:** These are formed in-

1. Anaplastic tumours
2. Hodgkin's disease: Reed-sternberg giant cell
3. Choriocarcinoma
4. Poorly differentiated astrocytoma (glioblastoma multiforme)

**Giant cells in virus infection:**

1. Giant cells of herpes simplex: Multiple giant cells are formed by fusion of virus infected epidermal cells.
2. Warthin – Finkeldey multinucleate giant cells of measles. These are usually seen in lymphoid tissues, lung and sputum and are pathognomonic of measles.

**Differences between Foreign body and malignant giant cells:**

Foreign body giant cells	Malignant giant cells
1. Found in chronic inflammation	1. Found in malignant tumours
2. Formed by fusion of macrophages	2. Formed by nuclear division without division of cytoplasm
3. Nuclei are small. Giant cells do not show characteristics of malignancy.	3. Giant cells show characteristics of malignancy.

(Ref: Khaleque's path)

**Q. Giant cells are a histological feature of:** (M. Phil, Diploma (DMC) - July-06)

- |                           |   |
|---------------------------|---|
| a) tuberculosis           | T |
| b) lobar pneumonia        | F |
| c) herpes virus infection | T |
| d) gummata                | F |
| e) talc granulomata       | T |

**Q. Langhans giant cells are a feature of :** (MD/MS (DMC)-01Ja)

- |                             |   |
|-----------------------------|---|
| A. Juvenile xanthogranuloma | F |
| B. Tuberculosis             | T |
| C. Foreign body reaction    | F |
| D. Chalazion                | F |
| E. Sarcoidosis              | T |

(Ref: Prof. Khaleque)

Help link: Langhans giant cells are a feature of TB.

**Q. Following inflammatory conditions predispose to cancer formation:** (BSMMU-M. Phil, Diploma, July-08)

- |                         |   |
|-------------------------|---|
| a) viral hepatitis      | T |
| b) chronic pancreatitis | T |
| c) acute appendicitis   | F |
| d) ulcerative colitis   | T |
| e) abscess              | F |
- [Ref: Robbins-9<sup>th</sup>, P-279; 8<sup>th</sup>, P-276]

**Q. Granulomata are classically associated with:** (PG-97Ja)

- |  |   |
|--|---|
| A. Chronic pulmonary beryllium disease | T |
| B. Ulcerative colitis                  | F |
| C. Crohn's disease                     | T |
| D. Sarcoidosis                         | T |
| E. Syphilitic aortitis                 | T |

a) True A number of chemical mediators act on the capillary endothelium to increase permeability thus allowing the escape of protein rich fluid into the area of acute inflammation. Amongst these various chemicals are histamine, a variety of kinins, prostaglandins and a number of complement components.

## Important MCQ of Inflammation

[Ref: Smiddy]

**Q. Acute inflammation can be caused by:**

- a) *Streptococcus pneumoniae*
- b) *Mycobacterium tuberculosis*
- c) *Neisseria meningitidis*
- d) *Mycobacterium leprae*
- e) *Borrelia vincenti*

Ans.

- a) **True** *Streptococcus pneumoniae* is the causal organism of lobar pneumonia.
- b) **True** Although *Mycobacterium tuberculosis* is more commonly associated with chronic inflammation, acute tuberculous inflammation does occur particularly following infection of the meninges or pleura.
- c) **True** *Neisseria meningitidis* is the causal organism of acute meningitis, a disease once referred to as 'spotted fever' because in the presence of meningococcal septicaemia a haemorrhagic rash occurs.
- d) **False** *Mycobacterium leprae* is never associated with acute inflammation. Two forms of leprosy occur, lepromatous and tuberculoid.
- e) **True** *Borrelia vincenti* is the causal agent of Vincent's angina, an acute inflammation of the gums and oropharynx. The organism itself is an anaerobic flexuous spirochaete with three to eight irregular coils. It is a normal commensal in the mouth.

**Q. The following agents produce an acute inflammatory reaction in unsensitised individuals:**

- a) lipopolysaccharide
- b) albumin
- c) ultraviolet light
- d) insulin
- e) carbon particles

Ans.

- a) **True** Lipopolysaccharides are the chemical structure of bacterial endotoxins. An immediate acute inflammatory reaction occurs following an intradermal injection of an endotoxin. If a subsequent intravenous injection of polysaccharide is administered some 24 hours later a local haemorrhagic reaction associated with tissue necrosis at the site of the previous intradermal injection occurs. (Schwartzmann reaction)
- b) **False** An intradermal injection of albumin does not cause an inflammatory reaction unless an individual has been previously sensitised.
- c) **True** Radiation injury which may be due to heat or ionising radiation in addition to ultraviolet light can cause an acute inflammatory reaction. The initial reaction is the triple response which follows histamine release.
- d) **False** Insulin does not cause an inflammatory reaction in unsensitised individuals
- e) **False** Carbon particles are biologically inactive although some of the carbon which is inhaled is engulfed by macrophages and is retained within the relatively immobile alveoli adjacent to the bronchioles, blood vessels and fibrous septa producing the blackening which is seen in nearly every adult lung of city dwellers at autopsy.

**Q. Normally the features of acute inflammation include:**

- a) vasoconstriction
- b) vasodilatation
- c) infarction
- d) haemolysis
- e) oedema

Ans.



- a) **True** The earliest change following the initiation of acute inflammation is constriction of small blood vessels.
- b) **True** The initial capillary constriction is rapidly followed by vasodilatation. This gives rise to the first part of the triple response described by Lewis, the red line'. This, in turn, is followed by arteriolar dilatation producing the flare' after which increased permeability of the small blood vessels causes the appearance of a weal'. This triple response can be readily reproduced by pricking histamine into the skin and can be blocked by antihistamines. It is, however, probably of little practical importance in acute bacterial inflammation.
- c) **False** Infarction is commonly due to the obstruction of an end artery, usually by an embolus. This causes a segmental area of tissue necrosis and whilst the necrotic area itself does not become inflamed the surrounding tissues show all the histological changes associated with inflammation.
- d) **False** The intravascular lysis of erythrocytes does not normally accompany acute inflammation. It may, however, develop due to the liberation of exotoxins by the infecting organisms, such as *Clostridium welchii* and *Streptococcus pyogenes*.
- e) **True** The exudation of fluid from the blood vessels in an inflamed area gives rise to swelling which is one of the cardinal signs of inflammation. The exudate is caused by several factors, including:
- (a) the hydrostatic pressure in the small blood vessels exceeding the osmotic pressure of the plasma proteins
  - (b) an increase in small vessel permeability caused by the chemical mediators of inflammation
  - (c) an inability of the lymphatics to remove the increased quantities of interstitial fluid.

**Q. The blood flow through acutely inflamed tissues is decreased by the following events:**

- a) increased cellular concentration in the blood flowing through the inflamed part
- b) loss of protein from the dilated capillaries
- c) aggregation of the red cells
- d) adherence of leucocytes to the capillary endothelium
- e) Lewis' axon reflex

Ans.

- a) **True** The cellular concentration of the blood in the capillaries and post-capillary venules of an inflamed tissue is increased. This occurs because as fluid escapes from the dilated blood vessels due to their increased permeability, the cellular concentration automatically increases and as a result causes an increase in blood viscosity.
- b) **False** Although protein loss does occur the fluid loss is greater, causing an elevation in the plasma protein concentration and hence an increase in viscosity.
- c) **True** The red cells aggregate into rouleaux which lead to sludging, a process first described by Kniseley. This further increases the viscosity of the blood.
- d) **True** The effective lumen of the post-capillary venules is greatly reduced by the adherence of the leucocytes to one another and to the endothelium of the capillaries and post-capillary venules.
- e) **False** It is doubtful whether the axon reflex is of any practical importance in the acute inflammatory process.

**Q. The magnitude of the exudate associated with acute inflammation depends upon:** (FCPS - Sur - 08Ja)

- a) changes in the endothelium of the capillaries and venules
- b) lymphocyte activation
- c) the osmotic pressure of the plasma proteins
- d) the plasma  $\text{Ca}^{++}$  level
- e) the plasma  $\text{K}^{+}$  level

Ans.

- a) **True** A number of chemical mediators act on the capillary endothelium to increase its permeability thus allowing the escape of protein rich fluid into the area of acute inflammation. Among these various chemicals are histamine, a variety of kinins, prostaglandins and a number of complement components.

- b) **False** There is no evidence that lymphocyte activation, which is important in cell-mediated immune reactions, delayed hypersensitivity and chronic inflammation, plays a major role in acute inflammation.
- c) **True** The osmotic pressure of the plasma and the inflammatory exudate is dependent upon the protein concentration. When the osmotic pressure in the exudate is higher than in the vessels, more fluid will be drawn from the vessels into the exudate.
- d) **False** There is no evidence, as yet, that plasma  $\text{Ca}^{++}$  levels affect the acute inflammatory response although the concentration of calcium does, however, play an important role in intracellular events. Thus the movement of extracellular calcium into the cell can activate a number of events through cyclic nucleotides.
- e) **False** There is no evidence that potassium concentration plays any part in the local inflammatory response. Hypo- or hyperkalaemia does, however, have important physiological effects, particularly on the myocardium.

**Q. The following cell types are involved in acute inflammation:**

- a) polymorphonuclear leucocytes      b) lymphocytes
- c) endothelial cells
- d) epithelioid cells
- e) mast cells

Ans.

- a) **True** The polymorphonuclear leucocyte is the chief cell involved in the acute inflammatory reaction. In a normal blood stream the leucocytes are confined to the central axial column, but as the blood flow slows as a result of increased vascular permeability, the white cells fall out of the central column and become marginated, so that in due course the capillary endothelium is paved with such cells. At this point, by inserting pseudopods between the endothelial cells, the polymorphs first squeeze between the endothelial cells and then the basement membrane to reach the extravascular space, after which they migrate towards the site of injury under the influence of chemotaxis. These processes are governed by a variety of chemical mediators. Migration is under the influence of a large number of adhesion receptors and chemotaxis is governed by a number of exogenous and endogenous substances which act as chemoattractants. The commonest exogenous attractants are the bacteria themselves and the endogenous mediators include components of the complement system especially C5, leukotrienes, especially B4, and cytokines chiefly IL8.
- b) **False** Lymphocytes play no major role in the early stages of acute inflammation. They are, however, of greater importance in chronic inflammation and are particularly important in those inflammatory processes which involve cell-mediated immunity.
- c) **True** Changes in the endothelium result in an increase in capillary permeability and the adherence of polymorphonuclear leucocytes to the walls of small blood vessels. Such changes are probably brought about by chemical mediators among which histamine, bradykinin and the prostaglandins appear to be important.
- d) **False** Epithelioid cells which are derived from mononuclear phagocyte cells are not seen in acute inflammation. They are associated with long standing chronic inflammation and are seen in the centre of granulomas caused by such agents as *Mycobacterium tuberculosis*.
- e) **True** Mast cells secrete histamine, serotonin, SRS-A and kallikrein, all of which play a role in the acute inflammatory process. Degranulation of the mast cells is an important step in the release of histamine from these cells, this chemical agent being one of the earliest chemical mediators found in acutely inflamed tissues.

**Q. The magnitude of leucocyte migration into an area infected with bacteria is governed by:**

- a) the type of organism causing the inflammatory lesion
- b) chemotaxins
- c) the C5a complement component
- d) the phosphatase levels in the inflamed area
- e) the formation of pus

Ans.

**a) True**

The intensity of the leucocytic infiltration into an infected lesion varies considerably. Some bacteria, notably the pyogenic organisms, such as *Streptococcus pyogenes*, *Staphylococcus aureus* and *Streptococcus pneumoniae* are associated with an intense leucocytic infiltration. Others, such as *Salmonella typhi* and *Clostridium welchii*, although causing severe inflammation, do not provoke a severe degree of leucocytic infiltration.

**b) True**

Chemotaxins are chemical substances which stimulate migration of the leucocytes in a particular direction. Identifiable chemotaxins include bacterial products; lysates of the polymorphonuclear cells and extracts from the inflamed tissues.

**c) True**

C5a is a product of reacted complement in certain circumstances it can be shown that complement depletion is associated with a decrease in leucocyte migration into an inflamed area.

**d) False**

Phosphatase levels play no part in the acute inflammatory process.

**e) True**

Lysates of the polymorphonuclear cells are very potent chemotactic agents when incubated with serum and it can therefore be assumed that pus formation increases leucocyte migration.

**Q. Prostaglandins are:**

- formed from complement
- vasodilators
- involved in clotting
- inhibited by azathioprine
- inhibited by aspirin

Ans.

**a) False**

Prostaglandins are derivatives of arachidonic acid which is released from mast cells and then metabolized by lipoxygenase or cyclooxygenase enzymes depending on the type of mast cell to lipid metabolites, including PGD<sub>2</sub>. A further source of prostaglandins is the macrophage. Complement is an enzymatic system of serum proteins activated by antigen-antibody reactions.

**b) True**

Vasodilatation and increased capillary permeability are produced by PGE<sub>1</sub> and PGE<sub>2</sub>, thus explaining the role of these compounds in acute inflammation. PGF<sub>2</sub> protects the tissues from this action.

**c) True**

Prostaglandins are involved in clotting because a powerful platelet aggregator, thromboxane A<sub>2</sub>, is formed from prostaglandins G<sub>2</sub> and H<sub>2</sub>. The enzymes involved are released when platelets become adherent to vessel walls.

**d) False**

Azathioprine does not inhibit the action of prostaglandins. It is, however, an immunosuppressive drug related to 6-mercaptopurine which is used in the treatment of diseases with an immunological basis including systemic lupus erythematosus, rheumatoid arthritis and Crohn's disease.

**e) True**

Aspirin inhibits the action of prostaglandins by the direct inhibition of their formation from the substrate arachidonic acid. This is thought to be the basis of its anti-inflammatory effect.

**Q. The main components of the pyogenic membrane are:**

- eosinophils
- capillary loops
- hyaluronidase
- polymorphonuclear leucocytes
- fibroblasts

Ans.

**a) False**

Eosinophil cells play no part in the acute inflammatory response which normally initiates the formation of a pyogenic membrane.

**b) True**

The proliferation of capillary loops is a characteristic feature of granulation tissue. When the original factor initiating the formation of the membrane, e.g. the pyogenic organism, has been eliminated either by the body's natural defence mechanisms or by the administration of antibiotics the capillary loops grow into the inflamed zone at up to 2 mm a day supported by ground substance.

**c) False**

Hyaluronidase is an enzyme produced by some bacteria such as the clostridia, the organisms responsible for gas gangrene. By destroying the connective tissue ground substance, it enables organisms to spread along tissue planes.

- d) True** Polymorphonuclear leucocytes migrate into the ground substance from the capillary loop in order to phagocytose bacteria. Peripheral to these cells may be plasma cells, lymphocytes and macrophages. all cells concerned with the natural defence mechanisms.
- e) True** Fibroblasts accompany the capillary loops and are dependent upon them for their oxygen supply. When the acute inflammatory reaction falters and the stage of healing has been reached, the fibroblasts lay down collagen.

**Q. The following are the chemical mediators involved in acute inflammation:**

- a) complement      b) histamine
- c) insulin
- d) bradykinin
- e) lymphokine

Ans.

- a) True** The C3a and C5a components of complement are powerful chemotactic agents attracting polymorphonuclear leucocytes to a site of acute inflammation. In addition these compounds also act as anaphylatoxins causing histamine release from the mast cells with the result that plain muscle contracts and vasoconstriction follows.
- b) True** Histamine liberated by the degranulation of mast cells is one of the most important causes of the changes seen in the early phase of acute inflammation, a phase which can be markedly depressed by the administration of antihistamines.
- c) False** This substance plays no known role in acute inflammation. It is secreted by the cells of the islets of Langerhans and is a major factor in controlling the circulating level of glucose. An increase in its secretion causes an enhanced uptake of glucose by the hepatocytes and a decrease in glucose absorption from the intestine.
- d) True** Bradykinin is a nonapeptide derived from a plasma euglobulin by the digestion of the latter by proteolytic enzymes. Among these are kallikrein which is present in the plasma as an inactive precursor which is activated by the Hageman factor. Bradykinin causes pain, erythema and increased vascular permeability and hence swelling of an acutely inflamed area.
- e) False** Lymphokines are not concerned with acute inflammation but are considered to be the mediators of delayed hypersensitivity. They are secreted by lymphocytes which have been activated by a specific antigen or mitogen. They are chemotactic to mononuclear cells, inhibit the migration of macrophages in vitro and cause delayed inflammatory reactions in the skin.

**Q. The following substances are involved in acute inflammation:**

- a) peptides      b) lectins
- c) plasmin
- d) LATS
- e) PGE<sub>1</sub>

Ans.

- a) True** Peptides composed of between 8 and 14 amino acid residues increase vascular permeability and hence increase the volume of exudate accompanying an acute inflammatory reaction. Such peptides are derived from protein in the exudate by the action of proteolytic enzymes derived from the plasma, tissue cells and polymorphonuclear leucocytes.
- b) True** Lectins are a group of transmembrane molecules belonging to the wider group known as selectins which are concerned with cellular adhesion. Hence they are an important part of the mechanism by which polymorphonuclear leucocytes adhere to the capillary endothelium, which is a necessary step prior to their migration into the extravascular space.
- c) True** Plasmin is intimately concerned with the acute inflammatory response. It is a proteolytic enzyme produced from the plasma plasminogen by the action of activators such as urokinase and streptokinase. Among the various actions of plasmin is its ability to break down fibrin to soluble degradation products, hence the use of activators in thrombolytic therapy. In addition it splits kininogen to form bradykinin and acts on the C3 component of complement to produce C3a and C3b. The former is a strong chemotactic agent and anaphylatoxin and the latter promote phagocytosis.

- d) **False** LATS, long acting thyroid stimulator is not involved in acute inflammation.  
 e) **True** This substance causes vasodilatation, increases capillary permeability and potentiates the activity of kinins. It, therefore, plays an important role in acute inflammation. PGE<sub>1</sub> is formed from the substrate arachidonic acid and the inhibition of its activity by aspirin and indomethacin is considered to be the basis of the antiinflammatory activity of these compounds.

**Q. Phagocytosis is promoted by:**

- a) hyaluronidase
- b) neuraminidase
- c) the hexose monophosphate shunt
- d) immunoglobulin
- e) complement

Ans.

- a) **False** Hyaluronidase plays no part in phagocytosis. It is, however, an important factor in the spread of infections caused by clostridia, staphylococci and streptococci all of which secrete this enzyme. Its action, is to break down hyaluronic acid which is a normal constituent of intercellular ground substance.  
 b) **False** Neuraminidase plays no part in phagocytosis. This substance is an enzyme produced by certain viruses and bacteria which splits a chemical bond between neuraminic acid and other sugars. Neuraminic acid is an important structural component of the surface glycoproteins of many cells.  
 c) **False** The hexose monophosphate shunt does not promote phagocytosis but it is a significant factor in causing the death of microorganisms following phagocytosis. This shunt is a powerful system of enzymes present in polymorphonuclear leucocytes and macrophages. It involves the activation of NADH and NADPH oxidases leading to the formation of powerful oxidising agents including hydrogen peroxide.  
 d) **True** Specific antibodies are important agents in the opsonisation of bacteria prior to phagocytosis.  
 e) **True** Complement components have an action which was known in the past as non-specific opsonisation. The conversion of C3 through either the classical or alternative pathway leads to the formation of C3b. This is recognised by specific cell receptors, by a process of immune adherence, leading to phagocytosis.

**Q. Microorganisms which have undergone phagocytosis are killed by:**

- a) lecithinase
- b) lysozyme
- c) lysosomal enzymes
- d) lymphokine
- e) hydrogen peroxide

Ans.

- a) **False** This enzyme has no action on microorganisms. It is one of the many enzymes produced by the clostridia, its specific action is to haemolyse erythrocytes by attacking their cell membranes.  
 b) **True** This enzyme, which is found in the polymorphonuclear leucocytes and at many other sites including tears, plays an important role in the destruction of microorganisms. It acts by destroying the muramic acid-N-acetyl-gluronic bond found in the glycopeptide coat of all bacteria.  
 c) **True** The lysosomal enzymes are a group of proteolytic and hydrolytic enzymes capable of digesting ingested microorganisms. High concentrations of these enzymes are secreted around ingested bacteria following fusion of lysosomes with the phagosome.  
 d) **False** Lymphokines play no direct part in the destruction of ingested microorganisms. However, these substances do activate the macrophages causing an increased production of lysosomal enzymes. Lymphokines are produced by the action of specific antigens or mitogens on primed T lymphocytes. They are important in the body's defence against certain microorganisms and are concerned with delayed hypersensitivity reactions.  
 e) **True** The killing of bacteria is largely accomplished by oxygen dependent mechanisms. The generation of oxygen metabolites due to the rapid activation of an oxidase (NADPH oxidase) which oxidises

NADPH (reduced nicotinamide-adenosine dinucleotide phosphate) and in the process, reduces oxygen to superoxide ion which is then converted to  $H_2O_2$ . The concentration of  $O_2^-$  of itself is insufficient to kill bacteria, but the granules of the neutrophils contain the enzyme myeloperoxidase which in the presence of  $Cl^-$  converts  $H_2O_2$  to HOCl. This then destroys the organism by binding covalently to bacterial constituents or by oxidation of proteins and lipids.

**Q. Pus contains:**

- a) lipids
- b) fibrin
- c) collagen
- d) plasma cells
- e) polymorphonuclear leucocytes

Ans.

- a) **True** Lipids are present in pus. They are derived from the plasma lipoproteins and from cellular breakdown products. Cholesterol may be found in old pus.
- b) **True** Pus contains fibrin because the activation of the coagulation system by the Hageman factor converts plasma fibrinogen into fibrin. The Hageman factor, Factor XII in the international classification of plasma coagulation factors, may be activated by kallikrein.
- c) **False** Collagen is not a constituent of pus although its breakdown products may be present due to the activity of enzymes known as collagenases. During healing collagen is laid down by fibroblasts.
- d) **False** Plasma cells are not normally found in the pus formed as a result of acute inflammation. Chiefly they are found, together with lymphocytes, in the lymph nodes, spleen and gut but they are also present in the organised granulomas which form in 'chronic inflammatory' lesions such as those which develop in rheumatoid arthritis.
- e) **True** The major cellular component of pus consists of living or dead polymorphonuclear leucocytes. These cells, when living, destroy ingested microorganisms, if these are the cause of the acute, inflammatory process. Polymorphonuclear leucocytes are attracted to the site of an acute inflammatory reaction by a variety of chemotactic agents, one of the most potent of which in vitro is a lysate of the polymorphonuclear leucocytes themselves.

**Q. Septicaemia is associated with:**

- a) bacteraemia
- b) toxæmia
- c) the multiplication of bacteria in the blood stream
- d) invasion of the blood stream by organisms multiplying elsewhere, e.g. the peritoneum
- e) multiple haemorrhagic foci in the tissues

Ans.

- a) **False** The term bacteraemia implies that bacteria are circulating but not multiplying in the blood stream. Nevertheless, a bacteraemia can be dangerous because any bacteria in the blood stream may settle in various parts of the body. For example, osteomyelitis in children is believed to follow bacteraemia, the responsible organism, commonly the *Staphylococcus aureus*, being deposited in the metaphysis of the long bones.
- b) **True** Profound toxæmia with high fever complicates a septicaemia because of the toxins liberated from the responsible bacteria. These toxins are pyrogenic of themselves and also cause the formation of pyrogens due to tissue damage.
- c) **True** The essential feature of a septicaemia is the multiplication of bacteria in the blood stream. An example is infection by the plague bacillus, *Yersinia pestis*.
- d) **True** In patients suffering from severe peritonitis caused by *Escherichia coli* the organisms in the blood stream are invaders from the inflamed peritoneal cavity.
- e) **True** Small haemorrhages commonly occur in various organs and tissues. These are caused either by the effects of the accompanying toxæmia on the endothelium or by metastatic foci of bacterial growth.

**Q. Necrosis occurs as a concomitant feature of chronic inflammation in:**

- a) leprosy
- b) tuberculosis
- c) syphilis
- d) actinomycosis
- e) coccidiomycosis

Ans.

- a) False** Necrosis is an inconspicuous feature of both tuberculoid and lepromatous leprosy. In the former epithelioid cell granuloma are the chief feature and leprosy bacilli are often difficult to find. In lepromatous leprosy, the essential lesions are formed of aggregates of mononuclear cells in which large numbers of the lepra bacilli can be found. The so-called 'lepra cells'. The pathogenicity of *Mycobacterium leprae* is so low that the mononuclear cells survive intense parasitism for long periods.
- b) True** The characteristic central caseous area of the typical tubercle caused by the *Mycobacterium tuberculosis* is due to necrosis: Caseous material contains high content of lipid and frequently a large number of bacilli. Aggregation of the follicles finally leads to the development of a tuberculous abscess and if liquefaction of the caseous material occurs the abscess begins to track through or along tissue planes to form in some cases the typical collar stud or psoas abscess.
- c) True** Coagulative necrosis and caseation is typical of the gumma formed in tertiary syphilis. How the necrosis is brought about remains doubtful but it may be due to ischaemia caused by the associated endarteritis obliterans.
- d) True** Necrosis is typical of an advanced actinomycotic lesion caused by the *Actinomyces bovis*, a bacterium related to the mycobacteria. The centre of an actinomycotic lesion consists of pus in which is found the sulphur granules which are grey-yellow in colour formed by colonies of filaments resembling fungal mycelia.
- e) True** Coccidiomycosis is a fungal infection. The pulmonary lesion is morphologically similar to that of tuberculosis being accompanied by central necrosis and causing micro-abscesses. These lesions frequently become calcified. Healing is associated with the development of a positive coccidioidin delayed hypersensitivity skin reaction.

**Q. The following belong to the mononuclear phagocyte system:**

- a) macrophages
- b) mast cells
- c) epithelioid cells
- d) fibroblasts
- e) Kupffer cells

Ans.

- a) True** The macrophage is the prototype of the cells belonging to the mononuclear phagocyte system. One of the most important characteristics of this cell which was first described by Metchnikoff is its ability to phagocytose foreign particulate and colloidal particles, but they are also important in processing antigen for lymphocyte recognition. It is the active non-specific effector cell in cell-mediated immunity and in host resistance to infection by facultative and obligate intracellular microorganisms, e.g. mycobacteria, protozoa and viruses. Macrophages are derived from bone marrow precursors via circulating monocytes and they are easily recognised histologically by observing their uptake of carbon particles.
- b) False** Mast cells are not a part of the MPS. They are the effector cells of IgE induced allergic reactions. Degranulated by antigen-antibody complexes they release histamine and other vasoactive substances such as serotonin and SRS-A.
- c) True** Epithelioid cells represent an activated form of the cells of the MPS; they are, however, poorly phagocytic but possess intense enzymatic activity. Such cells are found in the centre of immunologically induced tuberculoid-type granulomas and they may aggregate to form the Langhans type of giant cell.

- d) **False** Fibroblasts are not related to the mononuclear phagocyte system although they may be found in close proximity to macrophages and epithelioid cells in granulomas. The function of fibroblasts is to secrete collagen.
- e) **True** Kupffer cells are derived from precursor cells in the bone marrow that circulate as monocytes and then settle in the sinuses of the liver forming actively phagocytic cells.

**Q. Malignant disease may complicate the following chronic inflammatory diseases:**

- a) chronic osteomyelitis
  - b) Sarcoidosis
  - c) asbestosis
  - d) schistosomiasis
  - e) ulcerative colitis
- Ans.
- a) **True** Although extremely rare, squamous cell cancers were in the past seen in and around the skin sinuses associated with chronic osteomyelitis. The present rarity of the condition is due to the more effective treatment of osteomyelitis in the acute stage. The incidence of chronic osteomyelitis with the development of a large involucrum and chronically draining sinuses is extremely low in the Western World.
- b) **False** Sarcoidosis is not associated with malignant change.
- c) **True** Asbestosis is associated with the development of both squamous cell carcinoma and mesothelioma, 60% of the latter being due to exposure to asbestos, this relationship being first noted in South Africa. The fibre type associated with mesothelioma is crocidolite and the latent interval between exposure and the development of the tumour itself may be as long as 40 years. Such tumours occurring in the lungs are not necessarily associated with pulmonary fibrosis.
- d) **True** This disease is due to infestation with the dioecious trematodes, *chitosoma haematobium*, *mansi* and *japonicum*. In Egypt, the predominant infection is with *S. haematobium* and the adult parasites lie in the veins of the bladder. The eggs laid by the female pass into the submucosa and excite a granulomatous reaction which is later followed by metaplasia of the transitional cell urothelium to a squamous type. Squamous cell carcinoma then develops in a proportion of the victims, particularly infected Egyptians.
- e) **True** It is now well recognised that ulcerative colitis is a ' premalignant condition'. The incidence of malignancy increasing with the duration and totality of the disease being rarely seen in its more distal forms. At least one third of all cases with a history longer than 12 years develop cancer, usually multifocally.

**Q. Accumulation of macrophages is a prominent histological feature of the lesions produced by the following diseases:**

- a) leishmaniasis
  - b) extrinsic allergic alveolitis
  - c) Gaucher's disease
  - d) legionnaire's disease
  - e) Letterer-Siwe's disease
- Ans.
- a) **True** Both cutaneous leishmaniasis (oriental sore) and systemic leishmaniasis (kala-azar) are associated with lesions in which a particular feature is the large number of macrophages present. These contain the Leishman—Donovan bodies which are the amastigote form of the parasite.
- b) **False** One example of extrinsic allergic alveolitis is farmer's lung which is caused by the inhalation of the spores of *Micropolyspora faeni* found in mouldy hay. The lesion is caused by the deposition of immune complexes which activate complement giving rise to pulmonary fibrosis.
- c) **True** Gaucher's disease, an inherited condition, is due to a defect in the enzyme  $\beta$ -glucocerebrosidase. As a result large quantities of glucocerebroside accumulates in the macrophages especially of the spleen and to a lesser extent in the liver and lymph nodes of the thorax and abdomen. Such cells known as

the Gaucher cells are large up to 80 µm in diameter, with a pale cytoplasm in which is an irregular network of fibrils.

- d) False** A severe form of pyogenic bronchopneumonia with an almost lobar distribution, the disease occurs in epidemics and is believed to be caused by a Gram-negative bacillus, *Legionella*. The organism requires special cultures and tissue sections require staining with silver in order to demonstrate the pathogen.
- e) True** A form of 'histiocytosis X' which is a term applied to three conditions, Letterer-Siwe's disease, Hand-Schuller-Christian disease and eosinophil granuloma of bone. The condition referred to occurs in infancy and early childhood and runs a rapidly fatal course. It is characterized by hepatosplenomegaly, lymphadenopathy and multiple nodules in the skin and bone marrow. The affected organs show massive replacement by proliferated macrophage-like cells which are swollen, pale and contain phagocytosed debris.

**Q. Hyperplasia of the lymphoid tissue is a prominent feature in the following conditions:**

- a) toxoplasmosis
- b) leishmaniasis
- c) chronic dermatitis
- d) silicosis
- e) berylliosis

**Ans.**

- a) True** Lymph node enlargement, caused chiefly by a reactive hyperplasia of all components of the node, is a prominent feature of toxoplasmosis, caused by infection with the protozoan, *Toxoplasma gondii*. In addition the germinal centres are larger than those observed in similar infections and contain scattered accumulations of epithelioid type macrophages and B lymphocytes. The infection occurs in man due to accidentally ingesting oocytes from cat faeces or from eating incompletely cooked lamb or pork. Infection with this protozoan is especially serious in the foetus or in immunocompromised individuals.
- b) False** Specific hyperplasia of the lymphoid tissues does not occur in cutaneous leishmaniasis, otherwise known as oriental sore, caused by the protozoan, *Leishmania tropica*. In the systemic form of the disease, kala-azar caused by *Leishmania donovani*, hepatosplenomegaly occurs due to collections of macrophages which contain the Leishman-Donovan bodies. The latter are parasitic amastigotes.
- c) True** Chronic dermatitis is associated with dermatopathic lymphadenopathy in which there may be replacement of paracortical areas with macrophages and enlargement of the germinal centres.
- d) False** Silicosis does not appear to affect lymphoid tissue except to cause fibrosis. Fibrosis of inguinal lymphoid tissue is thought to be a cause of non-filarial elephantiasis in Ethiopia, as a result of absorption of silica through the skin.
- e) False** Beryllium oxide dust, when inhaled, produces progressive pulmonary fibrosis with associated loss of pulmonary function. The precise mechanism by which the pathological changes occur remains unknown, although a Type IV hypersensitivity reaction may play a part in the pathological process.

**Q. Giant cells are characteristically found in the pathological lesions associated with the following diseases:**

- a) actinomycosis
- b) schistosomiasis
- c) primary biliary cirrhosis
- d) lepromatous leprosy
- e) Hodgkin's disease

**Ans.**

- a) False** Actinomycosis is caused by a 'higher bacterium', the *A. israelii*. Infection with this organism produces chronic granulomatous abscesses most commonly in the facio-maxillary region. The abscess wall is heavily infiltrated with lipid laden macrophages and within the abscess are found mycelial masses between 0.2—2 mm in diameter, the sulphur granules', on the periphery of which are club-shaped

- swellings which are believed to be deposited by the host's tissue cells as a reaction to the presence of the organism.
- b) False** The granulomas associated with schistosomiasis form around the eggs which are laid by the female in the veins of the walls of the lower urinary tract in the case of *S. haematobium*. Occasional epithelioid cells, fibroblasts, lymphocytes and plasma cells are seen but giant cells are not a special feature.
- c) True** Primary biliary cirrhosis, a disease affecting middle-aged women rather than men, is of unknown aetiology. Pathologically a non-suppurative process affects the intrahepatic bile ducts. Miliary granuloma form in the portal areas associated with a heavy infiltration of lymphoid cells and some giant cells.
- d) False** In contradistinction to tuberculoid leprosy in which the lesions resemble those of tuberculosis, giant cells are rarely found in the lepromatous variety of this disease. In lepromatous leprosy the lesions consist of aggregates of macrophages which contain huge numbers of lepra bacilli. The bacilli tend not to be destroyed and to multiply within the cells which have ingested them.
- e) True** The characteristic cell of Hodgkin's disease is the Sternberg-Reed giant cell. This cell possesses double mirror image nuclei and is a particular feature of the pleomorphic cellular infiltrate which replaces the normal lymphoid tissue. The cells are probably neoplastic cells derived from the mononuclear phagocyte system.

**Q. The following predispose to the development of tuberculosis:**

- a) HLA—B27** The histocompatibility antigen HLA-B27 is not associated with an increased predisposition to tuberculosis but is associated with a high incidence of ankylosing spondylitis and acute anterior uveitis.
- b) sarcoidosis** Tuberculosis is rarely associated with sarcoidosis and the tuberculin reaction is frequently negative. However, the pathological lesion in the lungs and lymph nodes resembles that of a tuberculoid granuloma but without any associated caseation.
- c) silicosis** There appears to be a synergism between Silicosis and tuberculosis and in the presence of the former the incidence of the latter is greatly increased. Once the mycobacterium becomes established the disease may rapidly progress terminating in tuberculous bronchopneumonia and miliary tuberculosis.
- d) avitaminosis D** Although vitamin D was used in the treatment of tuberculosis and particularly for lupus vulgaris, there is no evidence that a deficiency of this vitamin predisposes to the development of tuberculosis any more than a general state of malnutrition.
- e) malnutrition** Protein-calorie malnutrition results in low resistance to a wide range of infections. Children with kwashiorkor have a depressed tuberculin reactivity and a lowered resistance to infection with mycobacteria.

**Q. Direct evidence of immunological activity can be demonstrated in the following chronic inflammatory diseases:**

- a) lepromatous leprosy**
- b) tuberculoid leprosy**
- c) Silicosis**
- d) rheumatoid arthritis**
- e) asbestosis**

**Ans.**

- a) False** Granuloma associated with lepromatous leprosy consist of diffuse collections of macrophages, within which are large numbers of *Myco. leprae* cells in which the bacteria have undergone degeneration and become distended with a lipid substance derived from the capsule of the bacilli. These large fat-distended cells or globi retain eosinophilic fragments of the organism at their periphery and are a

diagnostic feature. No significant infiltration of lymphocytes or plasma cells occurs around these lesions and the lepromin test is negative.

**b) True** Tuberculoid leprosy causes a non-caseating epithelioid cell granuloma in which the typical lesion is surrounded by a dense cuff of lymphocytes, together with epithelioid cells which often form Langhans giant cells. The lepromin test is positive and evidence of T-lymphocyte activation can be found in vitro.

**c) False** Patients suffering from silicosis may develop auto-antibodies but these are not directly involved in the pathogenesis of the silicotic nodules which are formed from collagen. Colloidal silica is intensely toxic to macrophages and it is this damage, with the release of intracellular lysosomes, which appears to stimulate the intense fibroblastic activity.

**d) True** The microscopic appearance of the early lesions of rheumatoid arthritis is evidence of the immunological aetiology of this disease. Such lesions consist of a central area of necrosis and fibroblastic activity surrounded by a cuff of lymphocytes and plasma cells. The latter appear to produce the rheumatoid factor which is an IgM anti-immunoglobulin antibody.

**e) False** No evidence of immunological activity is seen in the lesions produced by asbestos, another silica containing material which in fibre form can react with the macrophage cell membrane to cause intense fibroblastic activity and collagen synthesis. When inhaled, the reactive lesion is found particularly around the terminal bronchioles as well as the air sacs.

**Q. Epithelioid cell granuloma formation is associated with the following diseases: (FCPS – Sur - 09Ja)**

- a) ulcerative colitis
- b) Crohn's disease
- c) chronic glomerulo-nephritis
- d) toxoplasmosis
- e) sarcoidosis

Ans.

**a) False** This condition, which is a chronic inflammatory disease of the colon, is not associated with granuloma formation. Characteristically the disease, in its later and more severe forms, is associated with mucosal denudation due to the coalescence of smaller ulcers which develop from crypt abscesses. Such ulceration seldom extends more deeply than the submucosa.

**b) True** In the early acute phase of this disease a non-specific infiltration of chronic inflammatory cells consisting of plasma cells, macrophages and eosinophil cells is present. In the later granulomatous stage epithelioid and multinuclear giant cells appear in sarcoid-like non-caseating follicles. The inflammatory process may extend through the whole thickness of the affected viscera, thus involving the peritoneal surface of the abdominal viscera; hence the development of internal fistulas. In the later stages fibrosis becomes increasingly prominent resulting in the development of strictures.

**c) False** Organised granulomas do not occur in this condition although fibrosis around the glomerular tufts leads to their deformation. This disease is attributed to chronic immune complex deposition.

**d) True** Small epithelioid cell granulomas may be a feature of the lesions of toxoplasmosis, a disease caused by the protozoan, *Toxoplasma gondii*. They may be found in the enlarged lymph nodes which typically occur in this infection.

**e) True** Sarcoidosis is a disease of unknown aetiology in which lesions found in the lungs and lymph nodes are typically non-caseating tuberculoid granulomas. Those may be followed by intense pulmonary fibrosis. The diagnosis can be made by the use of the Kveim test in which an extract of the spleen of an affected individual is injected intradermally into the patient under investigation. A positive test results in the development of an organised epithelioid cell granuloma within six weeks.

**Q. Organised epithelioid cell granulomas develop in the following infections:**

- a) leprosy
- b) syphilis
- c) ankylostomiasis
- d) ascariasis
- e) schistosomiasis

**Ans.**

- a) **True** Epithelioid granulomas develop in the tuberculoid and not in the lepromatous form of leprosy. In the former the granulomas are immunologically induced and the positive Mitsuda type of skin reaction which develops within 2 to 3 weeks of the intradermal injection of dead *Mycobacterium leprae* is also an epithelioid cell granuloma. In contrast the granulomas associated with lepromatous leprosy are not immunologically induced, contain no epithelioid cells and the Mitsuda test is negative.
- b) **True** Gummas are nodular masses of syphilitic granulation tissue varying in size from scarcely visible lesions to masses several cm in size. The centre of the lesion undergoes necrosis and the periphery of the lesion is surrounded by an extensive zone of lymphocytes and plasma cells. Epithelioid cells may be found in follicles together with giant cells, the latter being smaller than the Langhans cells found in tuberculosis. Since the necrotic centre does not undergo softening, a gumma remains firm and rubbery.
- c) **False** Hookworm infection is not associated with granuloma formation. Transient pulmonary eosinophilia occurs in this condition if the larvae penetrate the intestinal wall and migrate through the lungs. Individuals suffering from ankylostomiasis usually have a severe anaemia due to the induced gastrointestinal haemorrhage.
- d) **False** Infection with the round worm, *Ascaris lumbricoides*, which is particularly prevalent in tropical areas, is not associated with granulomatous formation. Severe infection with round worms causes malnutrition and by entwining themselves into a bolus may cause intestinal obstruction or migrating into the common bile duct, cholangitis. The eggs hatch in the small intestine and having penetrated the gut wall are carried in the circulation to the lungs. Bursting through the alveolar capillaries, they travel upwards to the pharynx and are swallowed to develop into adult worms in the small intestine. Migration of the larvae to the lungs cause, pulmonary eosinophilia. Eosinophilia and a high IgE level are common in infected individuals.
- e) **True** The granulomas developing around schistosome eggs in the liver, intestines and bladder are typical immunologically induced epithelioid cell granulomas, usually associated with lymphocytes, plasma cells and eosinophils. Large numbers of fibroblasts are present and so these lesions are followed by intense fibrosis.

**Q. The following metals cause epithelioid cell granulomas:**

- a) beryllium
- b) chromium
- c) zirconium
- d) nickel
- e) iron

**Ans.**

- a) **True** The inhalation of beryllium is followed by a chronic inflammatory response in the lung. Commonly a non-caseating tuberculoid reaction is seen in the tissues. In addition to this action, beryllium is a contact sensitising metal.
- b) **False** Potassium dichromate does not cause granuloma formation but it does cause severe contact sensitivity. This particularly affects workers in the building trade because it may be a constituent of cement. Chromium used in orthopaedic implants can also cause sensitisation leading to local tissue breakdown and generalized skin rashes.
- c) **True** The metal itself is inert. However, zirconium lactate can cause non-caseating tuberculoid granulomas in the skin, the development of which are due to delayed hypersensitivity.
- d) **False** Nickel does not cause granuloma but like potassium dichromate it is a contact sensitizer. It may also give rise to local tissue reactions used in orthopaedic implants.
- e) **False** No tissue reaction occurs in response to iron or its various salts. However, in persons who have inhaled iron compounds over long periods an X-ray of the lungs gives a false impression that multiple granulomas have developed. No evidence of a chronic inflammatory lesion is, however, found in lung biopsies performed in such individuals.

## Tissue Repair

**Q. Stable cells include (BSMMU – Non-Residency – MD, MS, Basic science, Dentistry – July' 16)**

- |                                      |   |
|--------------------------------------|---|
| a) haemopoietic cells in bone marrow | F |
| b) hepatocytes                       | T |
| c) fibroblasts                       | T |
| d) endometrium                       | F |
| e) smooth muscle cells               | T |

**HELP LINK:**

**Labile (continuously dividing) tissues:** Cells of these tissues are continuously being lost and replaced by maturation from tissue stem cells and by proliferation of mature cells. Labile cells include

- hematopoietic cells in the bone marrow.
- the majority of surface epithelia, such as the stratified squamous epithelia of the skin, oral cavity, vagina, and cervix.
- the cuboidal epithelia of the ducts draining exocrine organs (e.g., salivary glands, pancreas, biliary tract).
- the columnar epithelium of the gastrointestinal tract, uterus, and fallopian tubes.
- the transitional epithelium of the urinary tract.

These tissues can readily regenerate after injury as long as the pool of stem cells is preserved.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-101)

**■ Quiescent (or stable) tissues:**

Cells of these tissues are quiescent (in the G0 stage of the cell cycle) and have only minimal proliferative activity in their normal state. However, these cells are capable of dividing in response to injury or loss of tissue mass.

**Examples:**

- the parenchyma of most solid tissues, such as liver, kidney, and pancreas.
- endothelial cells, fibroblasts, and smooth muscle cells.

The proliferation of these cells is particularly important in wound healing. With the exception of liver, stable tissues have a limited capacity to regenerate after injury.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-101)

**■ Nondividing (permanent) tissues:**

The cells of these tissues are considered to be terminally differentiated and nonproliferative in postnatal life.

**Examples:** The majority of neurons and cardiac muscle cells belong to this category. Thus, injury to the brain or heart is irreversible and results in a scar, because neurons and cardiac myocytes cannot regenerate. Limited stem cell replication and differentiation occur in some areas of the adult brain, and there is some evidence that heart muscle cells may proliferate after myocardial necrosis. Nevertheless, whatever proliferative capacity may exist in these tissues, it is insufficient to produce tissue regeneration after injury. Skeletal muscle is usually classified as a permanent tissue, but satellite

cells attached to the endomysial sheath provide some regenerative capacity for muscle. In permanent tissues, repair is typically dominated by scar formation.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-101)

**Q. Functions of platelet derived growth factor (PDGF) include (BSMMU – Residency – MD, MS, Basic science, Dentistry – March' 16)**

- |  |   |
|--|---|
| a) stimulation of platelet aggregation | F |
| b) inhibition of platelet aggregation  | F |
| c) stimulation of angiogenesis         | T |
| d) chemotaxis for macrophages          | T |
| e) prevention of wound contraction     | F |

**Help link:**

**FIGURE: Overview of healing responses after injury**

(Ref: Robbins & Cotran-9<sup>th</sup>, P-30)

**PDGF (Platelet derived growth factor)**

- Source: Macrophage, endothelial cells, smooth muscle cells, keratinocytes
- Functions:
  1. recruits smooth muscle cells,
  2. participate in stabilizing process
  3. Chemotactic for neutrophils, macrophage
  4. Activates and proliferations of fibroblasts, endothelial cells and other cells
  5. Stimulate ECM protein synthesis

(Ref. Robbins-8<sup>th</sup>, P-109)

**Q. Stable tissues/ cells** (BSMMU – Residency – MD, MS, Basic science, Dentistry – March' 16; Non-Residency – MD/MS, Basic science – July' 14; Residency – MD, Basic science – March' 14; M. Phil, Diploma (Non-Residency) – March-2012, DMC & others – MD/MS – March-2012)

- a) proliferate throughout life
- b) have a low level of replication
- c) can undergo rapid division in response to stimuli
- d) are non-dividing tissues
- e) are considered to be in the G<sub>0</sub> stage of the cell cycle

Ans. a) F b) T c) T d) F e) T

**Q. Following are the stable cells of the body** - (DMC – MD/ MS - January, 2010)

- |                     |   |
|---------------------|---|
| a. fibroblasts      | T |
| b. pancreatic cells | T |
| c. lymphoid tissue  | F |
| d. skeletal muscle  | F |
| e. osteoblasts      | T |

**Q. Stable cells/ tissues:** (BSMMU - M. Phil, Diploma, July-07)

- |   |   |
|---|---|
| a) proliferate throughout life                                    | F |
| b) have a low level of replication                                | T |
| c) can undergo rapid division in response to stimuli              | T |
| d) are non-dividing tissue  | F |
| e) are considered to be in the G <sub>0</sub> stage of cell cycle | T |

**Q. Labile cells are** (BSMMU - M. Phil, Diploma, July-04)

- A. Continuously proliferating cells.
- B. Proliferated in response to stimuli
- C. Parenchymal cells of glands
- D. Surface epithelia of oral cavity
- E. In G<sub>0</sub> phase of cell cycle.

Ans.

- A. True (Labile cells continue proliferate throughout life by continuing the cell cycle from one mitosis to the next)
- B. True (Cell proliferation is largely controlled by signals from microenvironment which either stimulate or inhibit cell proliferation)
- C. False (Parenchymal cells of liver, kidney and parcreas are quiescent or stable cells)
- D. True (Surface epithelia such as stratified squamous surface of the skin, oral cavity, vagina & cervix, the lining mucosa of all secretory ducts of the glands e.g. Salivary glands, biliary tract & uterus are labile cells)
- E. False (Stable cells are considered to be in the G<sub>0</sub> stage of the cell cycle but can be stimulated to enter G<sub>1</sub>)

## Wound healing & Tissue Repair

**Repair**, sometimes called **healing**, refers to the restoration of tissue architecture and function after an injury. (By convention, the term repair is often used for parenchymal and connective tissues and healing for surface epithelia, but these distinctions are not based on biology and we use the terms interchangeably.) Critical to the survival of an organism is the ability to repair the damage caused by toxic insults and inflammation. Hence, the inflammatory response to microbes and injured tissues not only serves to eliminate these dangers but also sets into motion the process of repair.

**Repair** of damaged tissues occurs by two types of reactions: regeneration by proliferation of residual (uninjured) cells and maturation of tissue stem cells, and the deposition of connective tissue to form a scar.

- **Regeneration.** Some tissues are able to replace the damaged components and essentially return to a normal state; this process is called **regeneration**.

Regeneration occurs by proliferation of cells that survive the injury and retain the capacity to proliferate, for example, in the rapidly dividing epithelia of the skin and intestines, and in some parenchymal organs, notably the liver. In other cases, tissue stem cells may contribute to the restoration of damaged tissues. However, mammals have a limited capacity to regenerate damaged tissues and organs, and only some components of most tissues are able to fully restore themselves.

- **Connective tissue deposition (scar formation).** If the injured tissues are incapable of complete restitution, or if the supporting structures of the tissue are severely damaged, repair occurs by the laying down of connective (fibrous) tissue, a process that may result in scar formation. Although the fibrous scar is not normal, it provides enough structural stability that the injured tissue is usually able to function. The term fibrosis is most often used to describe the extensive deposition of collagen that occurs in the lungs, liver, kidney, and other organs as a consequence of chronic inflammation, or in the myocardium after extensive ischemic necrosis (infarction). If fibrosis develops in a tissue space occupied by an inflammatory exudate, it is called organization (as in organizing pneumonia affecting the lung).

(Ref: Robbins & Cotran-9<sup>th</sup>, P-100)

Healing is the replacement of destroyed cells & tissues by the proliferation of viable cells either by similar cells or connective tissue.

Or,

Healing is usually a tissue response –

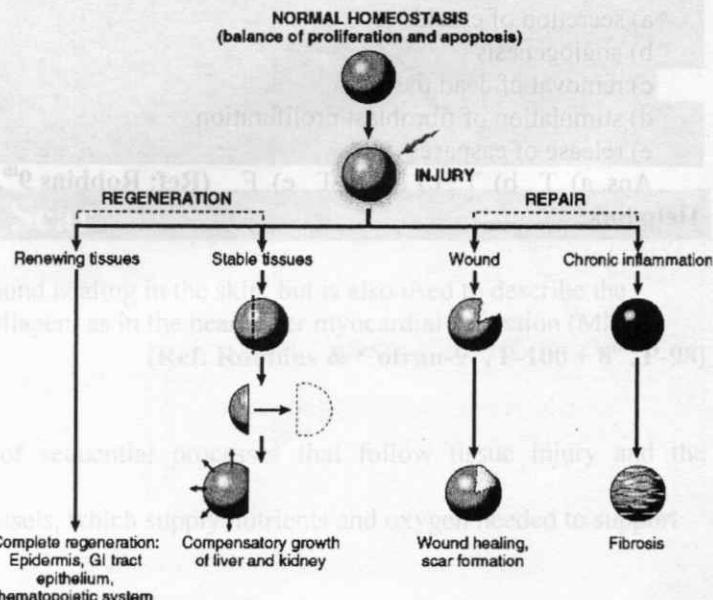
1. to a wound (commonly in the skin)
2. to inflammatory processes in internal organs or
3. to cell necrosis in organs incapable of regeneration.

(Ref: Robbins & Cotran-7<sup>th</sup>, P-88)

Or,

■ **Types:**

1. Regeneration
2. Repair
3. Fibrosis



**FIGURE: Overview of healing responses after injury**

(Ref: Robbins & Cotran-8<sup>th</sup>, P-80)

**Mechanism of healing:**

**A. Regeneration:** If tissue injury is not severe or chronic, healing can be accomplished by regeneration.

**B. Repair:** The main healing process is repaired by deposition of collagen and other ECM components causing the formation of a scar. Repair by connective tissue deposition includes the following basic features:

- Inflammation
- Angiogenesis
- Migration and proliferation of fibroblasts
- Scar formation
- Connective tissue remodeling

**C. Fibrosis:** By extensive deposition of collagen.

## KEY CONCEPTS

**Repair by Regeneration**

- Tissues are classified as labile, stable, and permanent, according to the proliferative capacity of their cells.
- Continuously dividing tissues (labile tissues) contain stem cells that differentiate to replenish lost cells and maintain tissue homeostasis.
- Cell proliferation is controlled by the cell cycle, and is stimulated by growth factors and interactions of cells with the extracellular matrix.
- Regeneration of the liver is a classic example of repair by regeneration. It is triggered by cytokines and growth factors produced in response to loss of liver mass and inflammation. In different situations, regeneration may occur by proliferation of surviving hepatocytes or repopulation from progenitor cells.

(Ref: Robbins & Cotran-8<sup>th</sup>, P-80, 98, 99)

**Mechanism of repair:** Repair by connective tissue deposition includes the following basic features –

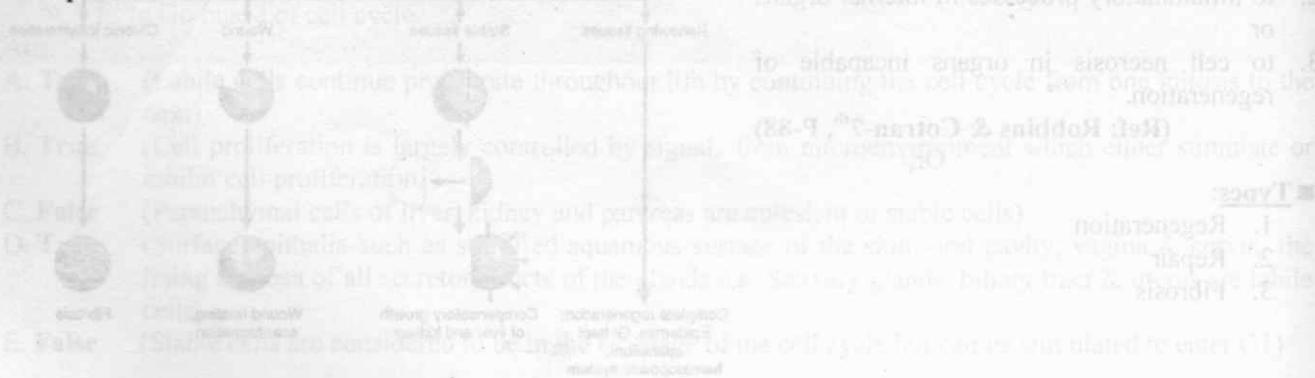
1. Inflammation
2. Angiogenesis
3. Migration and proliferation of fibroblasts
4. Scar formation
5. Connective tissue remodeling.

(Ref: Robbins & Cotran-9<sup>th</sup> + 8<sup>th</sup>, P-79, 80, 98)

**Q. Role of macrophages in tissue repair are (BSMMU – Diploma - Dentistry – July' 18)**

- a) secretion of cytokines
- b) angiogenesis
- c) removal of dead tissue
- d) stimulation of fibroblast proliferation
- e) release of caspases

Ans. a) T b) T c) T d) T e) F (Ref: Robbins 9<sup>th</sup>, P-104)

**Help link:**

(Ref: Robbins & Cotran-8<sup>th</sup>, P-80)

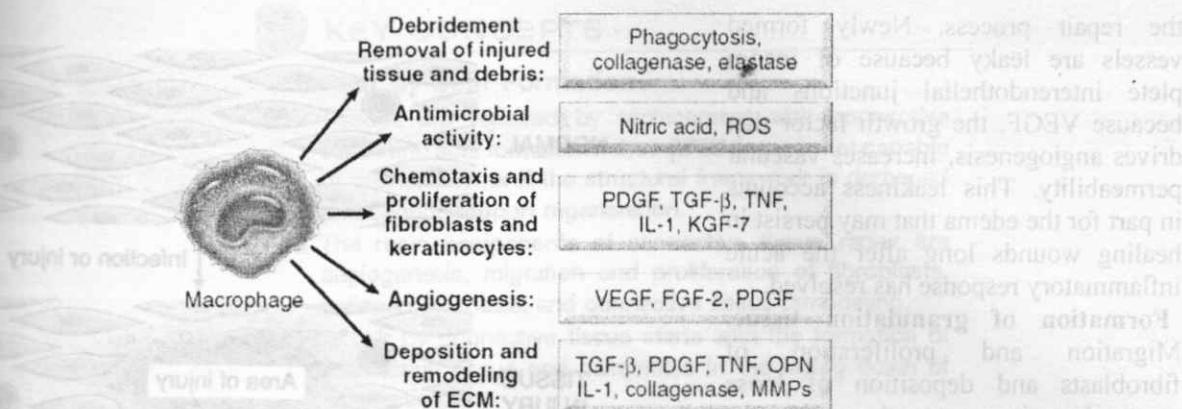


FIGURE 3-22 Multiple roles of macrophages in wound healing. Macrophages participate in wound debridement, have antimicrobial activity, stimulate chemotaxis and the activation of inflammatory cells and fibroblasts, promote angiogenesis, and stimulate matrix remodeling and synthesis. ROS, reactive oxygen species.

**Q. Cells that take part in wound healing are - (MD/MS (DMC)-09Ja)**

- a. polymorphs      T
- b. monocytes      T
- c. macrophages    T
- d. fibroblasts       T
- e. epithelium       T

**HELP LINK:**

#### Cells take part in wound healing

- Vascular endothelial cell
- Neutrophil
- Fibroblast
- Eosinophil
- Small blood vessel
- Lymphocyte
- ECM
- Monocyte
- Macrophage
- Epithelial cells
- Mast cell

## Scar

The term scar is most often used in connection to wound healing in the skin, but is also used to describe the replacement of parenchymal cells in any tissue by collagen, as in the heart after myocardial infarction (MI).

(Ref: Robbins & Cotran-9<sup>th</sup>, P-100 + 8<sup>th</sup>, P-98)

#### Steps of repair by Scar Formation:

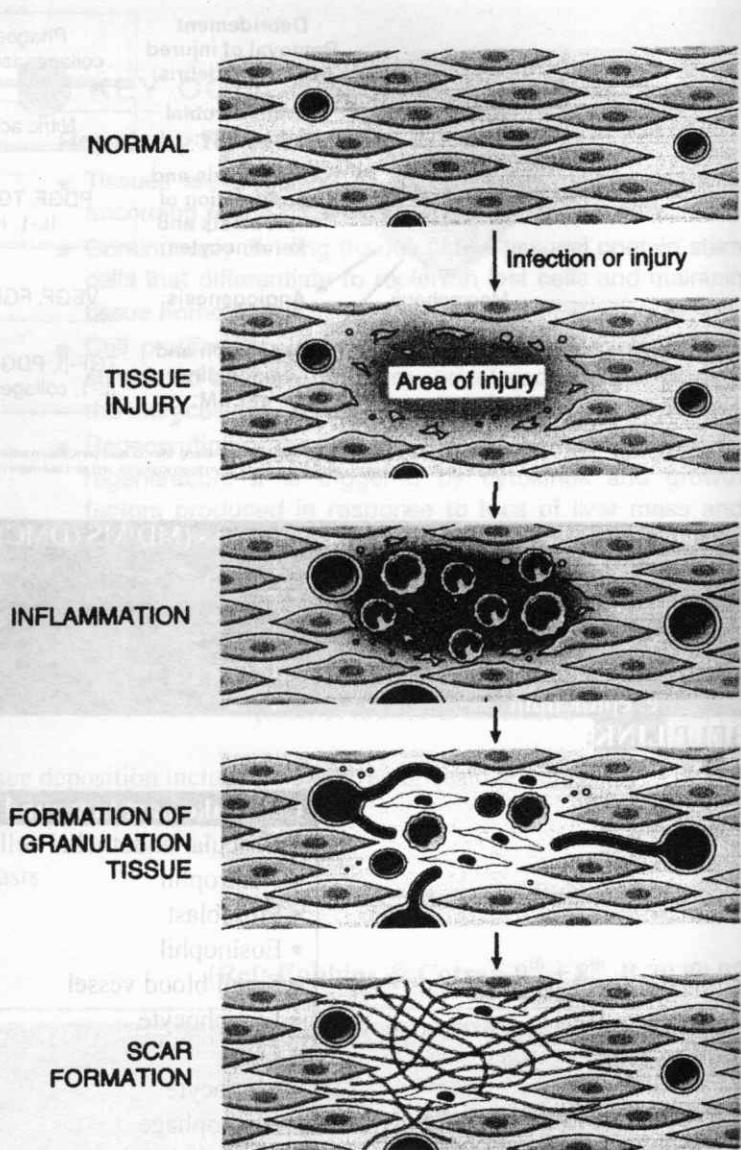
Repair by connective tissue deposition consists of sequential processes that follow tissue injury and the inflammatory response:

- **Angiogenesis** is the formation of new blood vessels, which supply nutrients and oxygen needed to support

the repair process. Newly formed vessels are leaky because of incomplete interendothelial junctions and because VEGF, the growth factor that drives angiogenesis, increases vascular permeability. This leakiness accounts in part for the edema that may persist in healing wounds long after the acute inflammatory response has resolved.

- **Formation of granulation tissue.** Migration and proliferation of fibroblasts and deposition of loose connective tissue, together with the vessels and interspersed leukocytes, form granulation tissue. The term granulation tissue derives from its pink, soft, granular gross appearance, such as that seen beneath the scab of a skin wound. Its histologic appearance is characterized by proliferation of fibroblasts and new thin-walled, delicate capillaries (angiogenesis), in a loose extracellular matrix, often with admixed inflammatory cells, mainly macrophages. Granulation tissue progressively invades the site of injury; the amount of granulation tissue that is formed depends on the size of the tissue deficit created by the wound and the intensity of inflammation.

- **Remodeling of connective tissue.** Maturation and reorganization of the connective tissue (remodeling) produce the stable fibrous scar. The amount of connective tissue increases in the granulation tissue, eventually resulting in the formation of a scar, which may remodel over time.



**Figure: Steps in repair by scar formation.** Injury to a tissue, such as muscle (which has limited regenerative capacity), first induces inflammation, which clears dead cells and microbes, if any. This is followed by the formation of vascularized granulation tissue and then the deposition of extracellular matrix to form the scar.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-103)

muscle (which has limited regenerative capacity), first induces inflammation, which clears dead cells and microbes, if any. This is followed by the formation of vascularized granulation tissue and then the deposition of extracellular matrix to form the scar.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-103)

#### Events/processes of scar formation:

- a. Emigration and proliferation of fibroblast in the site of injury
- b. Deposition of ECM (extra-cellular matrix)
- c. Tissue remodeling,

(Ref: Robbins & Cotran-7<sup>th</sup>, P-110)

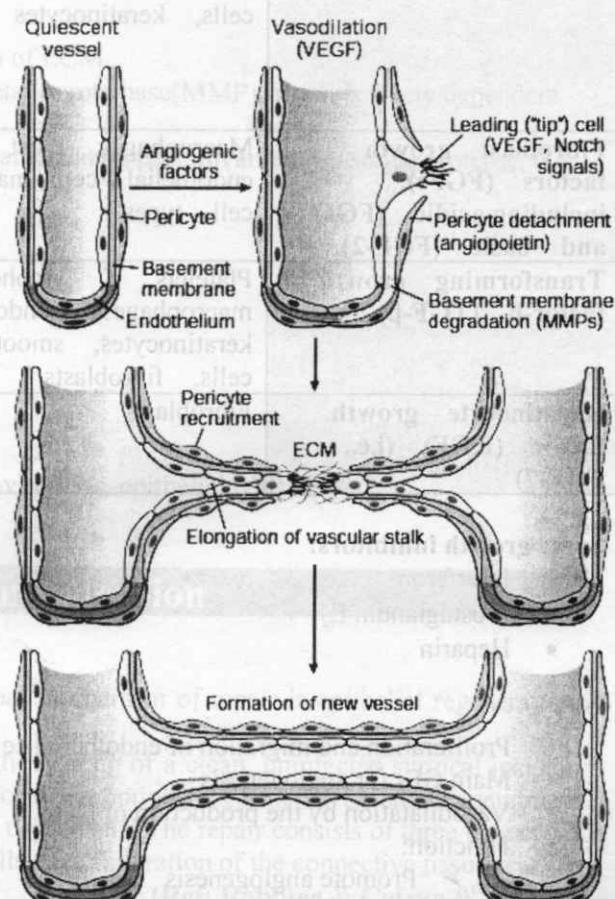
## KEY CONCEPTS

### Repair by Scar Formation

- Tissues are repaired by replacement with connective tissue and scar formation if the injured tissue is not capable of proliferation or if the structural framework is damaged and cannot support regeneration.
- The main components of connective tissue repair are angiogenesis, migration and proliferation of fibroblasts, collagen synthesis, and connective tissue remodeling.
- Repair by connective tissue starts with the formation of granulation tissue and culminates in the laying down of fibrous tissue.
- Multiple growth factors stimulate the proliferation of the cell types involved in repair.
- TGF- $\beta$  is a potent fibrogenic agent; ECM deposition depends on the balance between fibrogenic agents, metalloproteinases (MMPs) that digest ECM, and the tissue inhibitors of MMPs (TIMPs).

### Angiogenesis:

- Process of new blood vessels formation
- Induced by: Hypoxia inducible factors (HIF), VEGF, Angiopoietin 1, bFGF, PDGF, TGF-beta
- **Basic mechanisms:** sprouting of new vessels from the existing one, helped by NO, VEGF, bFGF, Recruitment of periendothelial cells,
- **Process of angiogenesis involves:**  
Signaling pathways:- cell-cell interactions, ECM proteins, tissue enzymes, Some GFs, Notch pathways, ECM proteins, enzymes



**Fig: Angiogenesis**

### Healing by primary intention

When the injury intact - usually the epithelium of skin, the principle also called primary union or healing by first intention.

One of the simplest examples of this type of wound repair is the

approximated by surgical suture.

continuity and death of relatively few cells and connective

processes: inflammation, proliferation of epithelial and other cells

### Sequence of events in primary healing:

1. Wounding causes the rapid activation of coagulation cascade and clotting factors on the wound surface. A scab covering the wound is formed.

## Growth factors involved in wound healing

### Growth Factors and Cytokines Involved in Regeneration and Wound Healing:

Growth factors	Sources	Functions
<b>Epidermal growth factor (EGF)</b>	Activated macrophages, salivary glands, keratinocytes, and many other cells	<ul style="list-style-type: none"> <li>Mitogenic for keratinocytes and fibroblasts</li> <li>Stimulates keratinocyte migration</li> <li>Stimulates formation of granulation tissue.</li> </ul>
<b>Transforming growth factor <math>\alpha</math> (TGF-<math>\alpha</math>)</b>	Activated macrophages, keratinocytes, and many other cell types	Stimulates proliferation of hepatocytes and many other epithelial cells
<b>Hepatocyte growth factor (HGF) (scatter factor)</b>	Fibroblasts, stromal cells in the liver, endothelial cells	Enhances proliferation of hepatocytes and other epithelial cells; increases cell motility
<b>Vascular endothelial growth factor (VEGF)</b>	Mesenchymal cells	Stimulates proliferation of endothelial cells; increases vascular permeability
<b>Platelet-derived growth factor (PDGF)</b>	Platelets, macrophages, endothelial cells, smooth muscle cells, keratinocytes	Chemotactic for neutrophils, macrophages, fibroblasts, and smooth muscle cells; activates and stimulates proliferation of fibroblasts, endothelial, and other cells; stimulates ECM protein synthesis
<b>Fibroblast growth factors (FGFs), including acidic (FGF-1) and basic (FGF-2)</b>	Macrophages, mast cells, endothelial cells, many other cell types	Chemotactic and mitogenic for fibroblasts; stimulates angiogenesis and ECM protein synthesis
<b>Transforming growth factor-<math>\beta</math> (TGF-<math>\beta</math>)</b>	Platelets, T lymphocytes, macrophages, endothelial cells, keratinocytes, smooth muscle cells, fibroblasts	Chemotactic for leukocytes and fibroblasts; stimulates ECM protein synthesis; suppresses acute inflammation
<b>Keratinocyte growth factor (KGF) (i.e., FGF-7)</b>	Fibroblasts	Stimulates keratinocyte migration, proliferation, and differentiation

(Ref: Robbins & Cotran-9<sup>th</sup>, P-19)

### Some growth inhibitors:

- Interferon
- Prostaglandin E<sub>2</sub>
- Heparin

### VEGF:

- Proliferation and migration of endothelial cells
- Main GFs for angiogenesis
- Vasodilatation by the production of NO
- Function:
  - Promote angiogenesis
  - Increased vascular permeability
  - Stimulate endothelial cell migration and proliferation
  - Induces hyperplasia of the lymphatic vasculature

(Ref: Robbins & Cotran-9<sup>th</sup>, P-110)

**What are the GFs for angiogenesis:**

- VEGF-A, bFGF-2, Angioprotein 1 and 2, PDGF(recruits smooth muscle cells, participate in stabilizing process), TGF-beta

**Deposition of connective tissue:**

- migration and proliferation of fibroblasts into the site of injury,
- deposition of ECM.

**Transforming growth factors (TGF-beta):**

- Most important cytokine for the synthesis and deposition of connective tissue proteins
- Produced by : alternatively activated macrophages
- Regulated by: post-transcriptional activation of latent TGF-beta (but not transcription of genes)
- Functions:
  - ✓ stimulate fibroblast migration and proliferation,
  - ✓ synthesis of collagen and fibronectin,
  - ✓ decrease degradation of ECM by inhibition of metalloproteinases,
  - ✓ not only in scar formation but also fibrosis in lung, liver, kidneys that follows chronic inflammation.
- It is an antiinflammatory cytokines that limit and terminate inflammatory process by inhibit lymphocyte proliferation and other leukocytes.

**Remodeling of connective tissue**

- Should be balanced between synthesis and degradation of ECM
- Degradation of ECM and collagen solely by matrix metalloproteinase(MMP) which is solely dependent on ZINC.
- Substances which degrade ECM: neutrophil elastase, cathepsin G, plasmin and other serine protease, but they are not dependent on ZINC.

**Regarding MMP:**

- Types:
  1. Interstitial collagenase (mmp 1,2, 3)
  2. Gelatinases (MMP-2,9)
  3. Stromelysin (MMP-3,10,11)
  4. Proteoglycans,
  5. Lamini, fibronectin, amorphous collagen
- Produced by: fibroblast, macrophage, neutrophils, synovial cells, epithelial cells
- Regulated by: GFs, cytokines.

## Primary & secondary intention

**Healing by primary intention:**

When the injury involves only the epithelial layer, the principal mechanism of repair is epithelial regeneration, also called primary union or **healing by first intention**.

One of the simplest examples of this type of wound repair is the healing of a clean, uninfected surgical incision approximated by surgical sutures. The incision causes only focal disruption of epithelial basement membrane continuity and death of relatively few epithelial and connective tissue cells. The repair consists of three connected processes: inflammation, proliferation of epithelial and other cells, and maturation of the connective tissue scar.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-106)

**Sequence of events in primary healing:**

1. Wounding causes the rapid activation of coagulation pathways, which results in the formation of a blood clot on the wound surface. A scab covering the wound is formed.

**2. Within 24 hours:** Neutrophils are seen at the incision margin, migrating toward the fibrin clot.

**3. In 24-48 hours:**

- Epithelial cells from both edges have begun to migrate and proliferate along the dermis, depositing basement membrane components as they progress.
- The cells meet in the midline beneath the surface scab, yielding a thin but continuous epithelial layer that closes the wound.

**4. By day 3:**

- Neutrophils are largely replaced by macrophages.
- Granulation tissue formation.
- Presence of collagen fibres in the margins of the incision.
- Further thickening of epidermis by proliferation of epithelial cells.

**5. By day 5:**

- Neovascularization is maximal.
- Incisional space is filled with granulation tissue.
- Collagen fibrils become more abundant and begin to bridge the incision.
- The epidermis recovers its normal thickness.

**6. During the second week:**

- There is continued accumulation of collagen and proliferation of fibroblasts.
- The leukocyte infiltrate, edema, and increased vascularity are substantially diminished.

**7. By the end of the first month:**

- Formation of scar by the cellular connective tissue devoid of inflammatory infiltrate.
- Permanent loss of dermal appendages
- Tensile strength of the wound increases with time.

(Ref: Robbins & Cotran-8<sup>th</sup>, P-106-107)

#### ■ Healing by Secondary intention:

When cell or tissue loss is more extensive, such as in large wounds, abscesses, ulceration, and ischemic necrosis (infarction) in parenchymal organs, the repair process involves a combination of regeneration and scarring. In healing of skin wounds by second intention, also known as **healing by secondary union**.

The inflammatory reaction is more intense, there is development of abundant granulation tissue, accumulation of ECM and formation of a large scar, and wound contraction by the action of myofibroblasts.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-107)

In healing by second intention, there are large tissue defects generate a larger fibrin clot that fills the defect (**hematoma formation**). Secondary healing differs from primary healing in several aspects:

1. The inflammatory reactions are more intense
2. Formation of abundant granulation tissue
3. Extensive collagen deposition
4. Substantial scar formation and thinning of the epidermis
5. Wound contraction (in case of large surface wounds).

(Ref: Robbins & Cotran-9<sup>th</sup>, P-108)

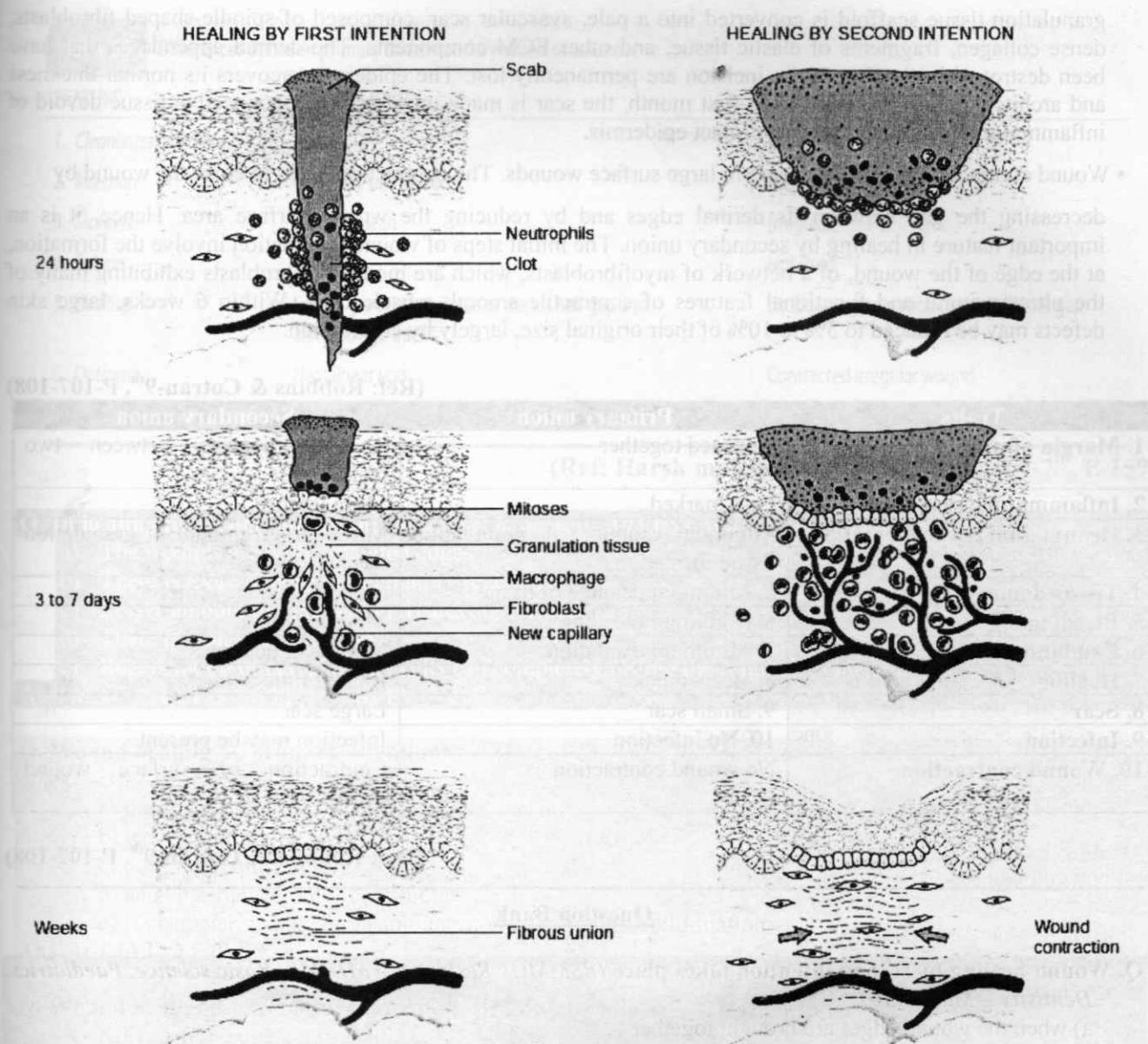


Figure 3-29 Steps in wound healing by first intention (left) and second intention (right). In the latter, note the large amount of granulation tissue and wound contraction.

#### Nice to know:

Secondary healing differs from primary healing in several respects:

- In wounds causing large tissue deficits, the fibrin clot is larger, and there is more exudate and necrotic debris in the wounded area. Inflammation is more intense because large tissue defects have a greater volume of necrotic debris, exudate, and fibrin that must be removed. Consequently, large defects have a greater potential for secondary, inflammation-mediated, injury.
- Much larger amounts of granulation tissue are formed. Larger defects require a greater volume of granulation tissue to fill in the gaps and provide the underlying framework for the regrowth of tissue epithelium. A greater volume of granulation tissue generally results in a greater mass of scar tissue.
- At first a provisional matrix containing fibrin, plasma fibronectin, and type III collagen is formed, but in about 2 weeks this is replaced by a matrix composed primarily of type I collagen. Ultimately, the original

granulation tissue scaffold is converted into a pale, avascular scar, composed of spindle-shaped fibroblasts, dense collagen, fragments of elastic tissue, and other ECM components. The dermal appendages that have been destroyed in the line of the incision are permanently lost. The epidermis recovers its normal thickness and architecture. By the end of the first month, the scar is made up of acellular connective tissue devoid of inflammatory infiltrate, covered by intact epidermis.

- Wound contraction generally occurs in large surface wounds. The contraction helps to close the wound by decreasing the gap between its dermal edges and by reducing the wound surface area. Hence, it is an important feature in healing by secondary union. The initial steps of wound contraction involve the formation, at the edge of the wound, of a network of myofibroblasts, which are modified fibroblasts exhibiting many of the ultrastructural and functional features of contractile smooth muscle cells. Within 6 weeks, large skin defects may be reduced to 5% to 10% of their original size, largely by contraction.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-107-108)

Traits	Primary union	Secondary union
1. Margin of wound	Aposed together	A gap persists between two margins.
2. Inflammatory reaction	Less marked	More intense.
3. Granulation tissue formation	Minimum amount of granulation tissue formation.	Much larger amount of granulation tissue is formed.
4. Tissue damage	5. Minimum damage of tissue.	Marked damage of tissue.
5. Bleeding	6. Minimum bleeding	More bleeding.
6. Exudation	7. Minimum exudation	Marked exudation.
7. Healing	8. Heals quickly	It takes time to heal.
8. Scar	9. Small scar	Large scar
9. Infection	10. No infection	Infection may be present
10. Wound contraction	No wound contraction	Contraction of surface wound occurs.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-107-108)

### Question Bank

**Q. Wound healing by second intention takes place (BSMMU –Residency - MD/MS, Basic science, Paediatrics, Dentistry – March '19)**

- when the wound edges are brought together
- in case of irreparable skin loss
- much more slowly than healing by first intention
- in infected wounds
- when the wound does not break apart

Ans: a) F b) T c) T d) T e) F

**Help link:**

**Table 5.9** Differences between primary and secondary union of wounds.

FEATURE	PRIMARY UNION	SECONDARY UNION
1. Cleanliness of wound	Clean	Unclean
2. Infection	Generally uninfected	May be infected
3. Margins	Surgical clean	Irregular
4. Sutures	Used	Not used
5. Healing	Scanty granulation tissue at the incised gap and along suture tracks	Exuberant granulation tissue to fill the gap
6. Outcome	Neat linear scar	Contracted irregular wound
7. Complications	Infrequent, epidermal inclusion cyst formation	Suppuration, may require debridement

(Ref: Harsh mohan testbook of Pathology-7<sup>th</sup>, P-159)**Q. In healing by second intention:** (BSMMU – Residency – MD/MS – March'13)

- a) The wounds are with separated edges
- b) There is more intense inflammatory reactions
- c) Lesser amount of granulation tissues are formed
- d) There is wound contraction
- e) Regeneration of parenchymal cells can completely restore the original architecture

Ans: a) T    b) T    c) F    d) T    e) F

**Q. Wound healing by primary intention:** (BSMMU – M. Phil, Diploma (Non-Residency)–March-2012, DMC & others – MD/MS – March-2012)

- a) needs- clean wound such as surgical incision
- b) leaves minimal scar
- c) does not require suture
- d) can be achieved only if antibiotics used
- e) is characterized by large amount of granulation tissue formation

Ans. a) T b) T c) F d) F e) F

**Q. Wound healing by secondary intention-** (BSMMU – MD/MS - 05Ja)

- A. is seen in large gaping defects      T
- B. is achieved by granulation tissue      T
- C. is without scar formation      F
- D. are less likely to give rise to keloids      F
- E. is followed by wound contraction      T (*Wound contraction occurs in large surface wound after a lag of 2 to 3 days*)

**Bone repair****Stages of bone repair:**Stage - 1: **Hematoma** is formed immediately.Stage - 2: **Acute inflammation** due to trauma. Fluid exudate & neutrophil infiltration occurs.Stage - 3: **Macrophage activity** (Demolition phase). Neutrophils are replaced by monocyte infiltration & macrophage activity.Stage - 4: **Formation of granulation tissue.** By the end of the 1st week, hematoma is organizing. This is called procillus. Neovascularization & fibrogenesis occur from the periosteum & endosteum.Stage - 5: **Woven bone & cartilage formation.** Osteoblasts & chondroblasts are derived from periosteum & endosteum. The calcified hard tissue is called callus.

**Stage - 6: Lamellar bone formation.** Woven bone & cartilage are removed. Progressive calcification & Haversian system formation occurs.

**Stage - 7: Remodeling.** The original structure of bone is formed by remodeling process by osteoclastic removal & osteoblastic laying down of bone. The intermediate callus is converted into compact bone, the external callus is removed & the internal callus is hollowed out into a marrow cavity.

(Ref: Walter & Israel-7<sup>th</sup>, P-182-185)

**Q. The healing of the closed fracture may be associated with the following pathological consequences:**  
(BSMMU-M. Phil, Diploma, July-08)

- |                        |   |
|------------------------|---|
| a) myositis ossificans | T |
| b) pseudoarthrosis     | T |
| c) osteomyelitis       | F |
| d) osteosarcoma        | F |
| e) renal calculi       | T |

**Help link:**

#### Complications from Fractures:

##### A. Early complications:

###### Life-threatening complications

These include vascular damage such as disruption to the femoral artery or its major branches by femoral fracture, damage to the pelvic arteries by pelvic fracture. Patients with multiple rib fractures may develop pneumothorax, flail chest and respiratory compromise.

Hip fractures, particularly in elderly patients, lead to loss of mobility which may result in pneumonia, thromboembolic disease or rhabdomyolysis.

###### Local:

- Vascular injury.
- Visceral injury causing damage to structures such as the brain, lung or bladder.
- Damage to surrounding tissue, nerves or skin.
- Haemarthrosis.
- Compartment syndrome (or Volkmann's ischaemia).
- Wound Infection - more common for open fractures.
- Fracture blisters.

###### Systemic:

- Fat embolism.
- Shock.
- Thromboembolism (pulmonary or venous).
- Exacerbation of underlying diseases such as diabetes or coronary artery disease (CAD).
- Pneumonia.

##### B. Late complications of fractures

###### Local:

- Delayed union (fracture takes longer than normal to heal).
- Malunion (fracture does not heal in normal alignment).
- Non-union (fracture does not heal).
- Joint stiffness.
- Contractures.
- Myositis ossificans.
- Avascular necrosis.
- Algodystrophy (or Sudeck's atrophy).
- Osteomyelitis.
- Growth disturbance or deformity.

###### Systemic:

- Gangrene, tetanus, septicaemia.
- Fear of mobilising.

## Granulation tissue

**■ Definition:** Granulation tissue may be defined as the immature mesenchymal tissue with proliferation of fibrovascular tissue with inflammatory infiltrates mainly lymphocytes may be plasma cells. The term is derived from its pink, soft & granular appearance on the surface of the wound.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-103)

**■ Characteristics of granulation tissue:**

1. Pink, soft, granular appearance on the surface of the wound.
2. Easily bleed on touch due to rupture of new capillaries.
3. Insensible due to lack of nerve supply.
4. Resistant to infection as monocytes form a coat on the surface.

**■ Histological features of granulation tissue:**

1. Numerous newly formed capillaries. Vascular loops appear like hair pins (neovascularization)
2. Spindle shaped fibroblasts are present in large numbers (fibroblast proliferation).
3. Infiltration of macrophages, new neutrophils, lymphocytes & red cells.
4. Collagen fibres- pink stained present.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-103)

**■ Functions:**

1. Resorption of necrotic tissue, thrombi, fibrin etc.
2. Replacement of defected tissue in the skin or mucous membrane.
3. Localization or walling of an abscess.

**Phases/ stages of granulation tissue formation:**

1. **Phase of traumatic inflammation:** An exudates of fibrin and polymorphs develops. Haemorrhage also occurs and the blood clot contributes to the fibrin formation.
2. **Phase of demolition:** There is macrophage infiltration. Macrophages ingest particulate matter, either digesting or removing it.
3. **Ingrowth of granulation tissue:** Granulation tissue is formed by the proliferation and migration of the surrounding connective tissue elements; it is composed at first of capillary loops that begin to appear at 3 days, and cells that are termed fibroblasts or myofibroblasts. There are two stages in its formation:  
Stage of vascularization and subsequently a stage of devascularization.

(Ref: Walter & Israel-7<sup>th</sup>, P-168, 169)

**Factors hampering granulation tissue formation:**

1. Vitamin C deficiency (scurvy)
2. Glucocorticoid (steroid) administration
3. Protein starvation: Dietary protein deficiency

(Ref: Walter & Israel-7<sup>th</sup>, P-172)

### Question Bank

**Q. Granulation tissue is formed in the following conditions (BSMMU-Residency - Dentistry - March '19)**

- a) mucosal ulcer
- b) abscess
- c) scar tissue
- d) mucocele formation
- e) gingival hyperplasia

Ans. a) T b) T c) F d) F e) F

**Help Link:**

**Granulation Tissue Formation:**

- ✓ The term granulation tissue derives its name from slightly granular and pink appearance of the tissue.

- ✓ Each granule corresponds histologically to proliferation of new small blood vessels which are slightly lifted on the surface by thin covering of fibroblasts and young collagen.
- ✓ The following 3 phases are observed in the formation of granulation tissue:
  1. PHASE OF INFLAMMATION
  2. Phase of clearance
  3. Phase of ingrowth of granulation tissue

(Ref: Harsh Mohan pathology-7<sup>th</sup>, P-157)

**Q. Granulation tissue is found in (BSMMU – Residency - MD, MS, Basic Science, Dentistry - March' 17)**

- a) ulcer
- b) sinus tract
- c) scar
- d) abscess
- e) necrosis

**Ans. a) T b) T c) F d) T e) F**

**Q. Granulation tissue is composed of (BSMMU – Residency – MS - March' 17)**

- a) newly formed blood vessels
- b) epithelioid cells
- c) fibroblasts
- d) Langhan's giant cells
- e) loose extracellular matrix

**Ans. a) T b) F (epithelioid cells are found in granuloma, not granulation tissue)**

**c) T**

**d) F (Langhan's giant cells are found in tubercular granuloma)**

**e) T**

**Q. Granulation tissue (BSMMU – Diploma – Dentistry-July' 16)**

- a) is a feature of wound healing
- b) leads to malignant transformation
- c) is formed without any wound
- d) does not bleed on touch when it becomes healthy
- e) is an important part of wound healing

**Ans. a) T b) F c) F d) F e) T**

**Q. Granulation tissue is composed of (BSMMU – Non-Residency – MD/MS, Basic science – July' 14, 13)**

- a) newly formed blood vessels
- b) epithelioid cells
- c) fibroblasts
- d) Langhans type giant cells
- e) Loose extracellular matrix

**Ans. a) T b) F c) T d) F e) T**

**Q. Granulation tissue is found in the: (BSMMU – Residency – MD/MS – March'13)**

- a) Abscess wall
- b) Edge of a granuloma
- c) Anal fistula\
- d) Wound healing
- e) Tumour stroma

**Ans : a) T b) T c) T d) T e) F**

**Q. Granulation tissue is found in -(BSMMU – MD - January-11)**

- |                               |   |
|-------------------------------|---|
| a) abscess wall               | T |
| b) granulomatous inflammation | T |
| c) fistula tract              | T |
| d) congested tissue           | F |
| e) ulcer base                 | T |

**Q. Granulation tissue is -(BSMMU - M. Phil, Diploma July-06)**

- |  |   |
|--|---|
| a) Highly vascularized connective tissue | T |
| b) Composed of epitheloid cells          | F |
| c) Soft and fleshy                       | T |
| d) Oedematous in early stage             | T |
| e) A form of chronic inflammation        | T |

**Q. Granulation tissue (M. phil, Diploma (DMC) – 03Ju)**

- |  |   |
|--|---|
| a) Is a collection of epithelioid cells              | F |
| b) Contains numerous proliferating capillaries       | T |
| c) Is oedematous                                     | T |
| d) Is named so because of its microscopic appearance | F |
| e) Bleeds on touch                                   | T |

**Q. Granulation tissue is found in -(BSMMU-MS-01Ja)**

- |                                     |   |
|-------------------------------------|---|
| a) Ulcer base                       | T |
| b) Within the tubercular granulomas | F |
| c) Lining sinus tracts              | T |
| d) Organizing haematoma             | F |
| e) Edges of healing infarct.        | T |

## Wound strength

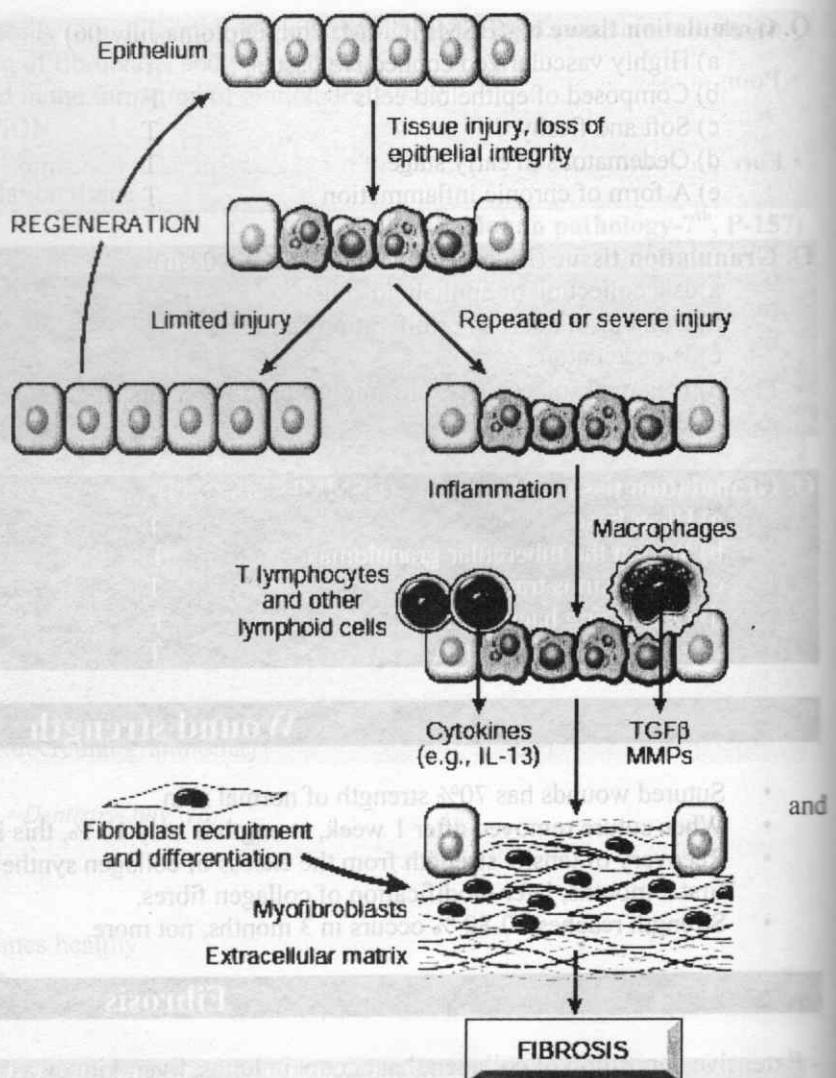
- Sutured wounds has 70% strength of normal skin
- When suture removed after 1 week, strength is only 10 %, this increase rapidly over the next 4 weeks
- Recovery of tensile strength from the excess of collagen synthesis over collagen degradation during the first 2 months, later modification of collagen fibres.
- Strength reaches 70-80 % occurs in 3 months, not more.

## Fibrosis

- Extensive deposition of collagen that occurs in lungs, liver, kidney as a consequence of chronic inflammation.
- Ischaemic necrosis/infarction in heart.
- Organization: if fibrosis develops in a tissue spaces occupied by an inflammatory exudate, eg: organizing pneumonia.
- Major cytokine involved TGF-beta
- **Fibrotic disorders:**
  1. liver cirrhosis,
  2. systemic sclerosis(scleroderma),
  3. Idiopathic pulmonary fibrosis,
  4. pneumoconiosis,
  5. drugs, radiation

- A) zinc  
B) progesterone  
C) estrogen  
D) oxytocin

Ans. a) P (delayed) - b) T - c) P (no effect on healing) - d) T - e) E (antidiarrhoeal agent, stimulates lactation - causes delayed wound healing)



**Fig:** Mechanisms of fibrosis. Persistent tissue injury leads to chronic inflammation and loss of tissue architecture. Cytokines produced by macrophages and other leukocytes stimulate the migration, proliferation of fibroblasts and myofibroblasts and the deposition of collagen and other extracellular matrix proteins. The net result is replacement of normal tissue by fibrosis.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-109)

## Factors affecting wound healing

Factors influencing wound healing:

### A. Systemic factors:

- **Diabetes** is a metabolic disease that compromises tissue repair for many reasons (Chapter 24), and is one of the most important systemic causes of abnormal wound healing.
- **Nutritional status** has profound effects on repair; protein deficiency, for example, and particularly vitamin C deficiency, inhibits collagen synthesis and retards healing.
- **Glucocorticoids (steroids)** have well-documented anti-inflammatory effects, and their administration may result in weakness of the scar due to inhibition of TGF- $\beta$  production and diminished fibrosis. In some instances, however, the anti-inflammatory effects of glucocorticoids are desirable. For example, in corneal infections, glucocorticoids are sometimes prescribed (along with antibiotics) to reduce the likelihood of opacity that may result from collagen deposition.

### B. Local factors:

- **Infection** is clinically one of the most important causes of delay in healing; it prolongs inflammation and potentially increases the local tissue injury.

- **Mechanical factors** such as increased local pressure or torsion may cause wounds to pull apart, or dehisce.
- **Poor perfusion**, due either to arteriosclerosis and diabetes or to obstructed venous drainage (e.g., in varicose veins), also impairs healing.
- **Foreign bodies** such as fragments of steel, glass, or even bone impede healing.
- **The type and extent of tissue injury** affects the subsequent repair. Complete restoration can occur only in tissues composed of stable and labile cells; even then, extensive injury will probably result in incomplete tissue regeneration and at least partial loss of function. Injury to tissues composed of permanent cells must inevitably result in scarring with, at most, attempts at functional compensation by the remaining viable elements. Such is the case with healing of a myocardial infarct.
- **The location of the injury** and the character of the tissue in which the injury occurs are also important. For example, inflammation arising in tissue spaces (e.g., pleural, peritoneal, synovial cavities) develops extensive exudates. Subsequent repair may occur by digestion of the exudate, initiated by the proteolytic enzymes of leukocytes and resorption of the liquefied exudate. This is called resolution, and in the absence of cellular necrosis, normal tissue architecture is generally restored. However, in the setting of larger accumulations, the exudate undergoes organization: granulation tissue grows into the exudate, and a fibrous scar ultimately forms.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-106)

#### **Question Bank**

**Q. Wound healing is delayed in (BSMMU – Non-Residency – MS, Basic Science – July' 19)**

- a) vitamin B deficiency
- b) starvation
- c) administration of glucocorticoid
- d) lack of blood supply
- e) early ambulation

Ans. a) F b) T c) T d) T e) T (Movement of the wound area may compress the blood vessels and separate the edges of wound area causes delay healing)

(Ref: Harsh Mohan Textbook of Pathology-7<sup>th</sup>, P-160 + Robbins-8<sup>th</sup>, P-160)

**Q. Factors causing delay in wound healing are (BSMMU – Non-Residency – Dentistry – July' 19)**

- a) infection
- b) ultraviolet light
- c) foreign bodies
- d) high protein diet
- e) vitamin C deficiency

Ans. a) T b) F (Exposure to ultraviolet light facilitates healing.) c) T d) F e) T

(Ref: Harsh Mohan Textbook of Pathology-7<sup>th</sup>, P-161)

**Q. Wound healing is delayed in (BSMMU – Residency - MS, Basic science – March' 19)**

- a) diabetes mellitus
- b) chronic renal failure
- c) infection
- d) vitamin C deficiency
- e) excess protein intake

Ans. a) T b) T (uremia) c) T d) T e) F (protein intake causes enhance wound healing)

**Q. Wound healing is enhanced by the administration of (BSMMU – Residency - Dentistry – March' 19)**

- a) cortisol
- b) zinc
- c) aldosterone
- d) oxygen
- e) vitamin C

Ans. a) F (delayed) b) T c) F (no effect on healing) d) T e) T (as well as vitamin A, deficiency of vitamin A causes delayed wound healing)

**Help Link:** The most common causes of tissue hypoxia are related to arterial occlusions or vasoconstrictors, hypotension, hypothermia and peripheral venous congestion. If there is a limited supply of oxygen to the wound, it prevents the production of collagen.

**Q. Wound healing is delayed by (BSMMU – Diploma - Dentistry – July' 18)**

- a) vitamin D deficiency
- b) starvation
- c) the administration of glucocorticoids
- d) reduced blood supply
- e) infection

Ans. a) F b) T c) T d) T e) T

**Q. Wound healing is enhanced by (BSMMU – Diploma - Dentistry – July' 18)**

- a) zinc
- b) vitamin B<sub>12</sub>
- c) vitamin C
- d) aldosterone
- e) cortisol

Ans. a) T b) F c) T d) F e) F

**Q. Wound healing is impaired by (BSMMU – Residency – MS, Basic Science, Dentistry – March' 18)**

- a) exogenous steroids
- b) thyroid hormone deficiency
- c) excess mobility of the affected part
- d) vitamin K deficiency
- e) presence of a foreign body

Ans. a) T b) F c) T d) F e) T

**Q. Factors impairing wound healing are (BSMMU – Non-Residency – MS – July' 17)**

- a) anaemia
- b) local haematoma
- c) hypoproteinaemia
- d) good circulation
- e) immobilization

Ans. a) T b) T c) T d) F e) F

**Q. Wound healing is enhanced by - (BSMMU – Non-Residency – MD, MS, Basic science – July' 15)**

- |              |                                   |
|--------------|-----------------------------------|
| a) cortisol  | F                                 |
| b) zinc      | T                                 |
| c) rest      | T                                 |
| d) oxygen    | T                                 |
| e) Vitamin D | F (very little effect on healing) |

**Q. Wound healing is enhanced by (BSMMU – Non-Residency – MS – July' 14)**

- a) zinc
- b) vitamin B<sub>12</sub>
- c) vitamin C
- d) aldosterone
- e) cortisol

Ans. a) T b) F c) T (causes cross linking of collagen) d) F e) F (anti-inflammatory effect)

**Q. Wound healing is enhanced by the administration of (BSMMU – Residency - MS, Basic science – March' 14; MD/MS – March' 13)**

- |                |   |
|----------------|---|
| a) cortisol    | F                                       |
| b) zinc        | T (Ref: Robins-9 <sup>th</sup> , P-443) |
| c) antibiotics | T                                       |
| d) oxygen      | T                                       |
| e) vitamin C   | T                                       |

**Help link:** Cortisol is helpful during corneal inflammation to reduce collagen deposition or inhibit scar formation.

**Q. Wound healing is delayed in (BSMMU – Non-Residency - MD/MS, Basic science – 13Ju)**

- |                                 |   |
|---------------------------------|---|
| a) old age                      | T |
| b) vitamin D deficiency         | F |
| c) infection                    | T |
| d) warm climate                 | F |
| e) the presence of foreign body | T |

**Q. Systemic factors that influence wound healing are: (BSMMU – Residency – MD/MS – March'13)**

- |                      |   |
|----------------------|---|
| a) Glucocorticoids   | T |
| b) Foreign bodies    | F |
| c) Diabetes Mellitus | T |
| d) Infection         | T |
| e) Nutrition         | T |

**Q. Risk factors for wound infection are: (BSMMU–M. Phil, Diploma – 11Ju, DMC & others –MD – 11Ju)**

- |                      |   |
|----------------------|---|
| a) malnutrition      | T |
| b) renal failure     | T |
| c) hypothyroidism    | F |
| d) diabetes mellitus | T |
| e) wound haematoma   | T |

**Q. The healing of a wound is delayed by: (BSMMU – MD – 11Ja)**

- |  |  |
|--|--|
| a) vitamin C deficiency                  |  |
| b) starvation                            |  |
| c) the administration of glucocorticoids |  |
| d) lack of blood supply                  |  |
| e) infection                             |  |

Ans.

- a) **True** Wound healing is dependent upon the synthesis of adequate amounts of collagen. This, in turn, is dependent upon the presence of vitamin C. Since man, monkey and the guinea-pig are unable to synthesize this vitamin its absence from the diet disturbs wound healing.
- b) **True** Starvation will affect wound healing but only when vitamin C deficiency has developed which inhibits collagen synthesis. Otherwise, even in markedly debilitated individuals, normal wound healing takes place.
- c) **True** The administration of excessive quantities of glucocorticoids causes a defect in collagen synthesis and also diminishes blood vessel formation.
- d) **True** A deficient blood supply leads to a lack of oxygen in the wound. This in turn diminishes fibroblastic activity because fibroblasts require an ambient O<sub>2</sub> tension of about 10mm Hg in order to function correctly.
- e) **True** Infection retards collagen synthesis, enhances the breakdown of pre-existing collagen and hence delays wound healing.

(Ref: Smiddy)

**Q. Following factors delay wound healing - (BSMMU - M-Phil, Diploma, July-'07)**

- |                             |  |
|-----------------------------|--|
| a) increased protein intake | F  |
| b) highly vascular tissue   | F  |
| c) glucocorticoids          | T  |
| d) vitamin C deficiency     | T  |
| e) obesity                  | T (because fatty tissue is less vascularized.) |

**Q. Wound healing of a wound is delayed by:** (DMC – M. PHIL, DIPLOMA - 05JULY)

- |                                      |   |
|--------------------------------------|---|
| a) Vitamin-D deficiency              | F |
| b) Malnutrition                      | T |
| c) Administration of glucocorticoids | T |
| d) Lack of blood supply              | T |
| e) Infection                         | T |

**Q. Factors that delay in wound healing:** (MD/MS (DMC)-05Ja)

- |                      |  |
|----------------------|--|
| a) Anabolic steroid  | F (used in athletes, e.g. testosterone)  |
| b) Scurvy            | T  |
| c) Cold weather      | T  |
| d) Ultraviolet light | F  |
| e) Copper deficiency | T (Ref: Robbins-9 <sup>th</sup> , P-443) |

**Q. Following factors favour wound healing.** (M. phil, Diploma – 03Ju)

- |                      |   |
|----------------------|---|
| a) Vitamin C         | T |
| b) Foreign bodies    | F |
| c) Diabetes mellitus | F |
| d) Glucocorticoids   | F |
| e) Infection         | F |

## Complications of wound healing

**Complications of wound healing:**

A. **Deficient scar formation:** Inadequate formation of granulation tissue or assembly of a scar can lead to 2 types of complications:

1. **Wound dehiscence:** Dehiscence or rupture of a wound is most common after abdominal surgery and is due to increased abdominal pressure. Vomiting, coughing, or ileus can generate mechanical stress on the abdominal wound.
2. **Ulceration:** Wounds can ulcerate because of inadequate vascularization during healing. For example, lower extremity wounds in individuals with atherosclerotic peripheral vascular disease typically ulcerate. Nonhealing wounds also form in areas devoid of sensation. These neuropathic ulcers are occasionally seen in patients with diabetic peripheral neuropathy.

B. **Excessive formation of the repair components:** can give rise to hypertrophic scars and keloids.

1. **Hypertrophic scars and keloids:** The accumulation of excessive amounts of collagen may give rise to a raised scar known as a **hypertrophic scar**; if the scar tissue grows beyond the boundaries of the original wound and does not regress, it is called a **keloid**.

Keloid formation seems to be an individual predisposition, and for unknown reasons this aberration is somewhat more common in African Americans. Hypertrophic scars generally develop after thermal or traumatic injury that involves the deep layers of the dermis. Collagen is produced by myofibroblasts, which persist in the lesion through the autocrine production of TGF-β, and the establishment of focal adhesions.

2. **Exuberant granulation:** It consists of the formation of excessive amounts of granulation tissue, which protrudes above the level of the surrounding skin and blocks re-epithelialization (this process has been called, with more literary fervor, **proud flesh**).

3. **Desmoids:** Incisional scars or traumatic injuries may be followed by exuberant proliferation of fibroblasts and other connective tissue elements that may, in fact, recur after excision. Called **desmoids**, or **aggressive fibromatoses**, these lie in the interface between benign proliferations and malignant (though low-grade) tumors. The line between the benign hyperplasias characteristic of repair and neoplasia is frequently finely drawn.

**C. Formation of contracture:** Contraction in the size of a wound is an important part of the normal healing process. An exaggeration of this process gives rise to *contracture* and results in deformities of the wound and the surrounding tissues. Contractures are particularly prone to develop on the palms, the soles, and the anterior aspect of the thorax. Contractures are commonly seen after serious burns and can compromise the movement of joints.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-109-110)

**D. Others:** A normally embedded in ground substance

1. Infection
2. Painful scar
3. Weak scar
4. Epidermoid cyst.
5. Neoplas



Fig: Hypertrophic scar

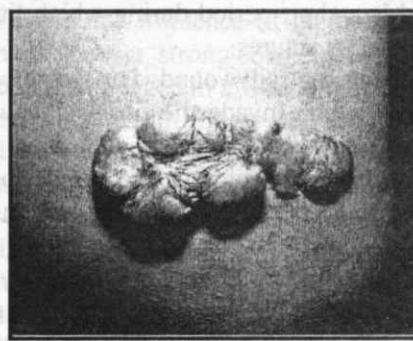


Fig: Keloid



Fig: Wound contracture

#### ■ Comparison of hypertrophic scar and keloid:

Features	Hypertrophic scar	Keloid
1. Genetic	Not familial	May be familial
2. Race	Not race related	Black > white
3. Sex	Female = male	Female > male
4. Age	Children	10 – 30 years
5. Borders	Remains within wound	Outgrows wound area
6. Natural history	Subsides with time	Rarely subsides
7. Site	Flexor surfaces	Sternum, shoulder, face
8. Aetiology	Related to tension	Unknown

## IMPORTANT MCQ OF WOUND HEALING

[Ref: Smiddy]

**Q. Wound healing is enhanced by the administration of:** (FCPS - Sur - 09Ja)

- a) cortisol
- b) zinc
- c) aldosterone
- d) oxygen
- e) vitamin C

Ans.

- a) **False** Cortisol impairs the synthesis of collagen and enhances its lysis and thus inhibits wound healing.
- b) **True** Zinc has been shown to accelerate the development of granulation tissue in a wound produced by the excision of a pilonidal sinus. The exact mechanism is unknown but there is evidence that it stabilises macromolecules and stimulates the biosynthesis of collagen.
- c) **False** Aldosterone has no effect in wound healing.
- d) **True** The fibroblast requires an ambient pO<sub>2</sub> of around 10 mm Hg in order to synthesize collagen and ground substance.

- e) True** Although the administration of vitamin C does not accelerate wound healing a deficiency causes a reduction in the synthesis of collagen and hence a lack of proper healing. If the deficiency of vitamin C severe and prolonged scurvy develops. In this condition even wounds which have previously healed break down.

**Q. The healing of an incised wound is associated with the following:**

- a lag phase
- a demolition phase
- a proliferative phase
- a contractile phase
- a maturation phase

**Ans.**

- a) True** The lag phase in a clean incised wound is a short period during which little cellular activity occurs and the integrity of the wound is maintained by sutures.
- b) True** This phase of minimal duration in a clean incised wound, is associated with the appearance of neutrophils at the margins of the incision which invade the fibrin clot, whilst the cut edges of the epidermis thicken as a result of mitotic activity of the basal cells and, within 48 hours, spurs of epithelial cells from the edges of the wound both migrate and grow along the cut margins of the dermis, fusing to form a continuous but thin layer. By the third day the neutrophils have been largely replaced by macrophages.
- c) True** By the fifth day the proliferative phase begins. In this phase great activity of the fibroblast-capillary system occurs which forms a thin layer of granulation tissue between the cut edges of the wound.
- d) False** Contraction is an essential feature of an open wound which is healing by secondary union (intention). Precisely how contraction occurs remains unknown although it may be caused by the fibroblasts of the granulation tissue, the myofibroblasts. The magnitude of contraction is greatest in sites where the skin is only loosely attached to the underlying tissues.
- e) True** This is the terminal phase of wound healing. During maturation the tensile strength of the wound gradually increases by intermolecular bonding between the collagen fibrils, the wound reaching about 80% of the tensile strength of unwounded skin. In addition the collagen is remodelled in response to mechanical stress placed on the wound.

**Q. The healing of a wound is delayed by: (BSMMU– MD – 11Ja)**

- vitamin C deficiency
- starvation
- the administration of glucocorticoids
- lack of blood supply
- infection

**Ans.**

- a) True** Wound healing is dependent upon the synthesis of adequate amounts of collagen. This, in turn, is dependent upon the presence of vitamin C. Since man, monkey and the guinea-pig are unable to synthesize this vitamin its absence from the diet disturbs wound healing.
- b) True** Starvation will affect wound healing but only when vitamin C deficiency has developed which inhibits collagen synthesis. Otherwise, even in markedly debilitated individuals, normal wound healing takes place.
- c) True** The administration of excessive quantities of glucocorticoids causes a defect in collagen synthesis and also diminishes blood vessel formation.
- d) True** A deficient blood supply leads to a lack of oxygen in the wound. This in turn diminishes fibroblastic activity because fibroblasts require an ambient O<sub>2</sub> tension of about 10mm Hg in order to function correctly.
- e) True** Infection retards collagen synthesis, enhances the breakdown of pre-existing collagen and hence delays wound healing.

**Q. Collagen, the ultimate source of the strength of a wound:**

- a) is formed by undifferentiated mesenchymal cells
- b) changes with the passage of time
- c) undergoes lysis as well as synthesis even when the total collagen content of the wound is remaining constant
- d) is broken down by the enzyme collagenase
- e) is normally embedded in ground substance

Ans.

- a) **False** Collagen is formed in the endoplasmic reticulum of the fibroblasts and excreted into the extracellular space in a monomeric form known as tropocollagen. When its synthesis is disturbed, as for example, in vitamin C deficiency, the precursor material collects and distorts the cell.
- b) **True** The procollagen, which is the precursor material excreted into the extracellular space, is hydroxylated under the influence of the enzyme procollagen hydroxylase. Polymerisation of the tropocollagen also occurs, strong covalent linkages being formed with neighbouring molecules.
- c) **True** The total amount of collagen in a wound may reach normal levels within 60 to 80 days but qualitative changes occur over a much longer period even though the total amount of collagen in the wound remains practically constant. Lysis is not confined to the wound but extends outwards from it for a variable distance. Should lysis be less intense than synthesis a hypertrophic or keloid scar may develop.
- d) **True** Collagenase is a naturally produced enzyme which is responsible for the breakdown of collagen. It has been shown in colonic anastomoses that up to 40% of the old collagen is lost in the first 4 to 6 days. This loss of collagen is believed to be responsible for many cases of anastomotic breakdown.
- e) **True** The collagen fibres are embedded in a ground substance, the chemistry of which is as yet incompletely understood. A major component appears to be large protein-polysaccharide complexes called proteoglycans. Ground substance appears to play a role in the organised precipitation of collagen of which there are 14 different types.

**Q. Post operative infection delays wound healing because:**

- a) the wound becomes packed with leucocytes
- b) many of the organisms involved produce spreading factors which may destroy the intercellular ground substance
- c) collagen is destroyed
- d) capillary loops fail to develop
- e) fibroblasts are diminished in number

Ans.

- a) **False** Although the majority of infected wounds become infiltrated with leucocytes these do not delay wound healing. However, if the supply of oxygen is deficient phagocytic function is impaired and their capacity to kill ingested bacteria is diminished.
- b) **False** Spreading factors do not play a significant role in the delay of wound healing. They are, however, of great importance in the spread of a number of infections particularly gas gangrene.
- c) **True** Not only does infection lead to the destruction of pre-existing collagen it also retards collagen synthesis. Even in a normal incised wound collagenolysis occurs for a distance of at least 5 mm on either side of the wound and is prominent for about 1 week.
- d) **False** Capillary loops, essential for the proper function of the fibroblasts continue to develop in the presence of infection.
- e) **False** Fibroblasts continue to be produced but the formation of collagen is retarded as collagen which is formed undergoes collagenolysis.

**Q. The following are the features associated with the healing of open wounds:**

- a) the formation of granulation tissue
- b) infection
- c) migration of the surrounding epithelium
- d) giant cell formation
- e) contraction

Ans.

- a) **True** Granulation tissue forms during the healing of both clean incised and open wounds, the difference is one of mass, less being formed during the healing of the former than the latter.
- b) **True** Some degree of infection is nearly always present when an open wound is present. In some circumstances this may be of great significance, e.g. infection of a burn wound by the haemolytic streptococcus may lead to a spreading infection and the destruction of any skin grafts which may be applied.
- c) **True** Migration of epithelial cells from the surrounding intact epithelium together with their proliferation leads to the formation of a sheet of cells which advances in a series of tongue-like projections beneath the remaining blood clot or exudate on the raw surface of the wound.
- d) **False** Giant cell formation will not be seen unless foreign material has been buried in the wound. This may then lead to the formation of foreign body giant cells.
- e) **True** Contraction is an important aspect of the healing of an open wound and it is most conspicuous when the skin is loose. It occurs to a remarkable extent in animals such as the rabbit. The mechanism bringing about contraction is still debatable, but it probably is caused by modified fibroblasts known as myofibroblasts which have an ultrastructure similar to smooth muscle cells. In rabbits, a large wound can be reduced to within 10% of its original size within 6 weeks by contraction.

**Q. Wound healing may be governed by the following:**

- trephones
- vitamin D
- chalone
- mineralocorticoids
- the availability of sulphur containing amino acids

Ans.

- a) **True** It has been suggested that the stimulus to wound healing is mediated by trephones liberated by damaged cells. Although a working hypothesis based on tissue culture studies, the existence of such substances has yet to be proven *in vivo*.
- b) **False** Vitamin D is of little importance in the healing of soft tissue wounds.
- c) **True** This is a second hypothesis. It has been postulated that normal tissues secrete a substance capable of depressing mitosis, a chalone, and that a wound, by removing some of this depressor substance, permits an increased level of mitotic activity. There is some *in vitro* experimental work in the rabbit supporting this hypothesis although no chemical substance acting in this manner has yet been identified.
- d) **False** Mineralocorticoids play no specific part in wound healing but are, of course, of great importance in maintaining the optimal milieu interieur without which normal body functions could not continue.
- e) **True** The presence of adequate amounts of sulphur containing amino acids such as methionine is essential for collagen synthesis: In well nourished individuals supplementing the diet with extra protein or additional vitamins, especially vitamin C, does not increase the rate of wound healing. The effects of protein and vitamin deficiency only become apparent in the starving animal.

**Q. Woven bone is found:**

- in bone forming in a model of cartilage
- in fracture haematomas
- in bones forming in sheets of differentiating mesenchyme
- replacing lamellar bone in healing fractures
- surrounding the ends of ununited fractures

Ans.

- a) **False** Bone formed in a previous model of cartilage is of a lamellar type. Most of the skeleton is made of lamellar bone which replaces the initial cartilage, hence the term endochondral ossification. Lamellar bone is characterized by the arrangement of the collagen bundles into parallel sheets either forming concentric Haversian systems or flat plates.

- b) **True** Woven bone with its irregular arrangement of collagen bundles and osteocytes is the first type of bone forming in a fracture haematoma. It is replaced later by mature, lamellar or adult bone which is finally remodelled as the fracture unites.
- c) **True** Bone formed in differentiating mesenchyme is of the woven variety. This occurs during the embryonic development of the bones of the vault of the skull, the mandible and the clavicle, these bones being referred to as membrane bones.
- d) **False** The converse is true. Woven bone precedes lamellar bone.
- e) **False** The ends of ununited fractures are eventually covered by cartilage and if the latter are surrounded by synovial cells a false joint or pseudarthrosis develops. At this stage union becomes impossible regardless of the duration of immobilisation.

**Q. The healing of a closed fracture may be associated with the following pathological consequences:**

(BSMMU-M. Phil, Diploma, July-08)

- a) myositis ossificans
- b) pseudoarthrosis
- c) osteomyelitis
- d) osteosarcoma
- e) renal calculi

Ans.

- a) **True** Immediately following injury a fracture haematoma forms and if the periosteum is torn, blood extends out into the surrounding tissues. Subsequent organisation and ossification leads to the development of myositis ossificans. This complication is particularly seen following fractures around the elbow joint and the pelvis.
- b) **True** The mesenchymal cells of the granulation tissue invading the fracture haematoma normally differentiate into bone forming osteoblasts which lay down woven bone. This is later replaced by lamellar bone. If, however, a fracture is imperfectly immobilised these cells may form fibrous tissue, cartilage and finally synovial cells with the result that a false joint develops. This is a well recognised complication of tibial fractures.
- c) **False** Infection of the fracture site is an extremely rare complication of an uncomplicated closed fracture. It might occasionally occur in patients suffering from multiple injuries in whom a septicaemia develops due to infection elsewhere in the body.
- d) **False** Although the external callus around the fracture site may lead to a considerable 'tumour' there is no evidence that fractures lead to an increased incidence of osteosarcoma.
- e) **True** Fractures involving long term immobilisation particularly in the recumbent position may lead to renal calculi. These are often called recency calculi and are due to the hypercalciuria which develops in an immobilised patient and the relative stagnation of urine in the lower most calyces of the kidney. In the past, when spinal tuberculosis was relatively common, and prior to the development of antituberculous drugs, such calculi frequently followed the prolonged recency necessary to treat the disease.

**Q. Ischaemic necrosis is a recognised complication of fractures of the following bones:**

- a) talus
- b) calcaneum
- c) scaphoid
- d) pisiform
- e) femoral head

Ans.

The answer is: 1, 3, 5 are **true** and 2 and 4 are **false**.

Ischaemic necrosis following fractures of the talus, scaphoid and femoral head is merely a reflection of the local peculiarities of the blood supply to the bones. Fracture lines running through these bones divorce one fragment from its blood supply with the result that ischemic necrosis occurs. In fractures of the femoral head the development of ischaemic necrosis leads to pain once weight bearing begins. Radiologically the affected part becomes denser than the surrounding normal bone.

## HEMODYNAMIC DISORDERS

### SAAG (serum albumin – ascites albumin gradient)

**Q. Causes of low serum ascites albumin gradient (BSMMU – Residency – Basic Science – March' 15)**

- a) constrictive pericarditis
- b) Budd-Chiari syndrome
- c) peritoneal carcinomatosis
- d) peritoneal tuberculosis
- e) nephrotic syndrome

Ans. a) F b) F c) T d) T e) T

**Q. High serum-ascites albumin gradient occurs in (BSMMU – Non-Residency – MD, Basic science – July' 14)**

- a) cirrhosis of liver
- b) constrictive pericarditis
- c) peritoneal carcinomatosis
- d) peritoneal tuberculosis
- e) nephrotic syndrome

Ans. a) T b) T c) F d) F e) F

**Help link:**

SAAG = serum albumin – ascites albumin gradient

A high gradient (SAAG >1.1 g/dL) indicates portal hypertension and suggests a nonperitoneal cause of ascites.

Transudative causes of ascites and High SAAG causes are equal. Venous outflow obstruction due to cardiac failure or hepatic venous outflow obstruction can also cause a transudative ascites, as indicated by an albumin gradient above 11 g/L but, unlike in cirrhosis, the total protein content is usually above 25 g/L.

(Ref: Davidson-22<sup>nd</sup>, P-939)

#### Old Classification

**Transudate (protein < 30g/l) causes:**

- Cirrhosis and portal hypertension
- Nephrotic syndrome
- Cardiac failure
- Budd-Chiari syndrome
- Myxodema.

**Exudate (protein > 30g/l) causes:**

- Intra-abdominal tuberculosis
- Pancreatitis.
- Hepatic or peritoneal malignancy

#### New Classification

**↑ SAAG (>1.1 g/dL) causes:**

- Cirrhosis
- Alcoholic hepatitis
- Schistosomiasis
- Fulminant hepatic failure
- Budd-Chiari syndrome
- Acute or chronic portal vein obstruction
- Cardiac diseases
- Spontaneous bacterial peritonitis secondary to cirrhosis.

**↓ SAGG (<1.1 g/dL) causes:**

- Nephrotic syndrome
- Protein losing enteropathy
- Peritoneal carcinomatosis
- Tuberculous peritonitis
- Pancreatic duct leak
- Biliary ascites.

(Ref: MRCP pass medicine-2016)

## Amyloid stain

- Congo red: gives apple green birefringens under polarized microscope
- Crystal violet stain: red-purple metachromasia
- Thioflavin T stain: silver blue fluorescence under UV light
- Standard toluidin blue (STB)
- IHC (immunohistochemistry) Many different
- PAS with increased
- Electrom microscopy

**Q. Amyloid reacts with the following stain (BSMMU -Residency - MD/ Basic science - March' 14)**

- |                     |   |
|---------------------|---|
| a) congo red        | T |
| b) thioflavin -T    | T |
| c) crystal violet   | T |
| d) Masson trichrome | F |
| e) Prussian blue    | F |

Ans.

- a) **True** The Congo red test for amyloid depends on the specificity of this dye for amyloid. Intravenously administered Congo red disappears rapidly from the circulation in amyloid disease due to its rapid conjugation with this material. Amyloid material stained with Congo red can be seen to best advantage when the tissue is examined in polarised light when a green birefringence can be seen. Biopsy material to establish the presence of amyloid is usually taken from the rectum, gums or kidney.
- b) **True** Thioflavine-T is a fluorochrome which reacts with amyloid. It is particularly useful for demonstrating small glomerular deposits.
- c) **True** Methyl violet is a metachromatic stain, staining normal tissue violet and amyloid pink.
- d) **False** Masson trichrome is for identification of muscle, collagen fibre, fibrin, erythrocyte.
- e) **False** Prussian blue is positive in hemosiderin and bone marrow iron in sideroblastic anaemia and iron.

## OEDEMA

Edema is the result of the movement of fluid from the vasculature into the interstitial spaces; the fluid may be protein-poor (transudate) or protein-rich (exudate).

(Ref: Robbins & Cotran-9<sup>th</sup>, P-115)

Or,

**Oedema** may be defined as an excessive extravascular accumulation of fluid.

**Anasarca** is a severe and generalized edema with widespread subcutaneous tissue swelling.

(Ref: Robbins & Cotran-8<sup>th</sup>, P-112)

### ■ Patho-physiological categories of edema:

#### 1. Increased Hydrostatic pressure:

##### a. Impaired venous return:

- Congestive heart failure
- Constrictive pericarditis
- Ascites (liver cirrhosis)
- Venous obstruction or compression

-Thrombosis

-External pressure (e.g. mass)

-Lower extremity inactivity with prolonged dependency

##### b. Arteriolar dilation:

- Heat
- Neurohumoral dysregulation

## **2. Reduced plasma osmotic pressure (Hypoproteinemia):**

- Protein-losing glomerulopathies (nephrotic syndrome)
  - Liver cirrhosis (ascites)
  - Malnutrition
  - Protein-losing gastroenteropathy

### **3. Lymphatic obstruction:**

- Inflammatory
  - Neoplastic
  - Post-surgical
  - Post-irradiation

#### **4. Sodium retention:**

- Excessive salt intake with renal insufficiency
  - Increased tubular reabsorption of sodium
    - Renal hypoperfusion
    - Increased renin-angiotensin-aldosterone secretion.

### **5. Inflammation:**

- Acute inflammation
  - Chronic inflammation
  - Angiogenesis

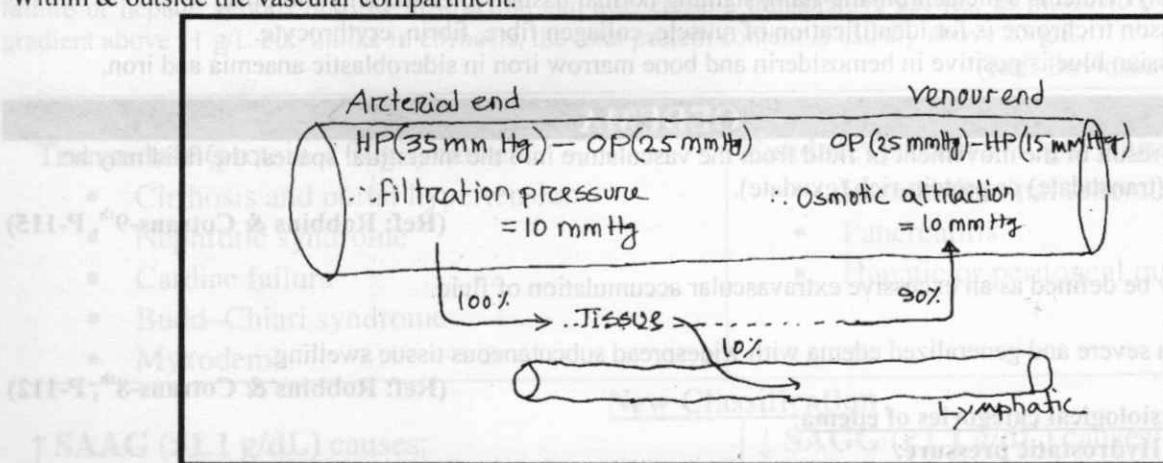
(Ref: Robbins & Cotrans-9<sup>th</sup>, P-114)

#### ■ Pathogenesis of non-inflammatory oedema:

The normal interchange of fluid is regulated by—

1. Hydrostatic pressure (HP) &
  2. Osmotic pressure (OP)

### E. Osmotic pressure ( $O_P$ )



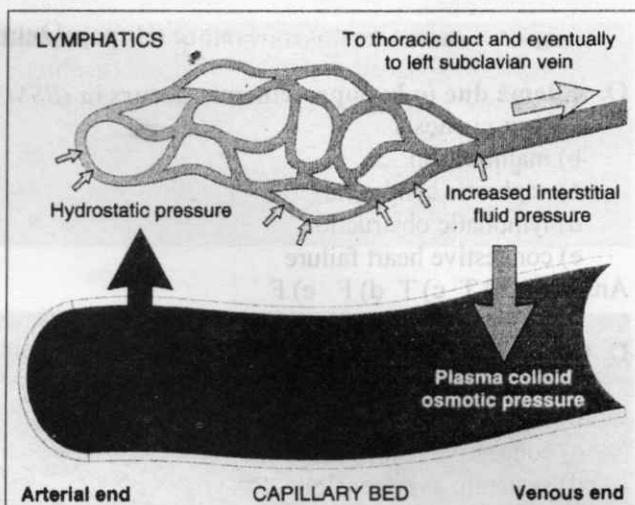
So, edema will occur when the following conditions are present.

- ↑ Hydrostatic pressure in blood vessels.
  - ↓ Plasma colloidal osmotic pressure.
  - Renal retention of Na & water.
  - Impairment in the flow of lymph.

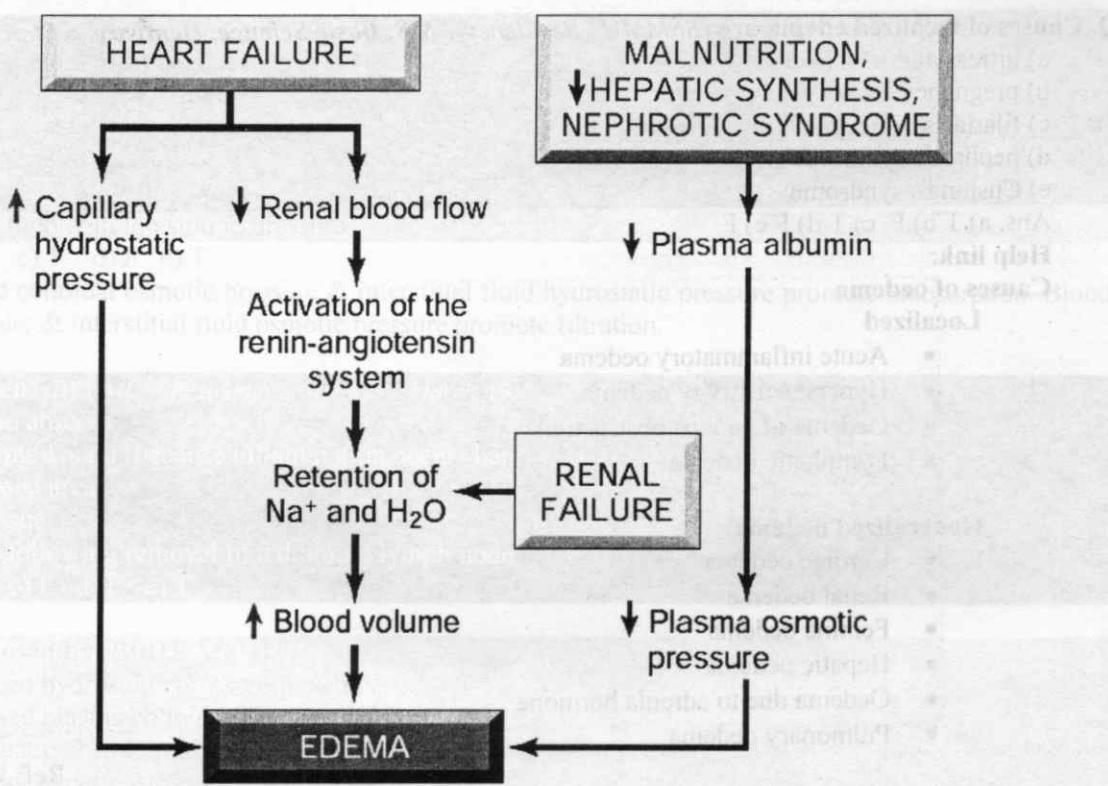
■ **Pathogenesis of inflammatory oedema:** Inflammatory edema is formed by the combined effect of-

1. **Increased vascular permeability**: An injurious agent → Alteration in vascular caliber. → Increase in blood flow. → Structural changes in the microvasculature → Escape of fluid, plasma proteins & leukocytes into the interstitial tissue or body cavities → edema.
  2. **Increased capillary hydrostatic pressure**: Vasodilatation → ↑ hydrostatic pressure → outflow of fluid from blood vessel into interstitial tissue & accumulation → exudates → edema.
  3. **Decreased plasma colloidal osmotic pressure in blood vessels** (Ref: Robbins & Cotran-9<sup>th</sup>, P-113-114)

**Figure: Factors influencing fluid movement across capillary walls.** Normally, hydrostatic and osmotic forces are nearly balanced so that there is little net movement of fluid out of vessels. Many different pathologic disorders are associated with increases in capillary hydrostatic pressure or decreases in plasma osmotic pressure that lead to the extravasation of fluid into tissues. Lymphatic vessels remove much of the excess fluid, but if the capacity for lymphatic drainage is exceeded, tissue edema results.



(Ref: Robbins & Cotran's-9<sup>th</sup>, P-114)



**Figure 4-2** Mechanisms of systemic edema in heart failure, renal failure, malnutrition, hepatic failure, and nephrotic syndrome.

- **Periorbital oedema**- severe renal disease
- **Pulmonary oedema**-increased weight of lung in 2-3 times, on cross sections, frothy blood tinged fluid mixed with air, oedema, and extravasated RBCs.
- **Brain oedema**- localized or generalized, narrow sulci and distended gyri due to compressed by the skull.

## **Question Bank**

**Q. Edema due to hypoproteinemia occurs in (BSMMU – Diploma - Dentistry – July' 18)**

- a) liver cirrhosis
  - b) malnutrition
  - c) nephrotic syndrome
  - d) lymphatic obstruction
  - e) congestive heart failure

Ans. a) T b) T c) T d) F e) F

**Q. Generalized edema develops in (BSMMU – Residency – MD, MS, Basic Science, Dentistry – March '18)**

- a) nephrotic syndrome
  - b) filariasis
  - c) congestive heart failure
  - d) systemic hypertension
  - e) cirrhosis of liver

Ans. a) T b) F c) T d) F e) T

**Q. Causes of localized edema are (BSMMU –Residency – MS, Basic Science, Dentistry – March' 18)**

- a) urticaria
  - b) pregnancy
  - c) filariasis
  - d) nephrotic syndrome
  - e) Cushing's syndrome

Ans. a) T b) F c) T d) F e) F

**Help link:**

## **Causes of oedema**

## Localized

- Acute inflammatory oedema
  - Hypersewnsitivity oedema
  - Oedema of venous obstruction
  - Lymphatic oedema

#### **Generalized oedema**

- Cardiac oedema
  - Renal oedema
  - Feminine oedema
  - Hepatic oedema
  - Oedema due to adrenal hormone
  - Pulmonary oedema

Ref: Walter and israel

**Q. Generalized body swelling with hypoalbuminemia occurs in patients suffering from (BSMMU –Residency – Dentistry – March '18)**

- a) protein losing enteropathy
  - b) cardiac failure
  - c) liver cirrhosis
  - d) protein calorie malnutrition
  - e) chronic lung disease

Ans. a) T b) F c) T d) T e) F

**Q. Forces causing outward movement of fluid at the arterial end of capillary are (BSMMU – Non-Residency – MD, MS, Basic Science & Dentistry – July' 17)**

- a) capillary hydrostatic pressure
- b) negative interstitial fluid pressure
- c) mean systemic filling pressure
- d) plasma colloid osmotic pressure
- e) interstitial fluid colloid osmotic pressure

Ans. a) T b) T c) F d) F e) T

**Q. Oedema due to hypoproteinemia occurs in (BSMMU – Residency - Dentistry - March' 17)**

- a) liver cirrhosis
- b) left heart failure
- c) radiation therapy
- d) nephrotic syndrome
- e) hypothyroidism

Ans. a) T b) F c) F d) T e) F

**Help link:** Other causes – malnutrition and protein losing gastroenteropathy.

**Q. Capillary filtration rate tends to increase when there is an increase in (BSMMU – Non-Residency – MD/MS, Basic science – July' 14)**

- a) plasma colloid osmotic pressure
- b) capillary hydrostatic pressure
- c) total peripheral resistance
- d) interstitial fluid hydrostatic pressure
- e) interstitial fluid colloid osmotic pressure

Ans. a) F b) T c) T d) F e) T

**Help link:** Blood colloidal osmotic pressure & interstitial fluid hydrostatic pressure promote reabsorption. Blood hydrostatic pressure & interstitial fluid osmotic pressure promote filtration.

**Q. Oedema is seen: (BSMMU – Residency – MD/MS – March'13)**

- a) Around an abscess
- b) In a healing wound (because inflammation occurs here)
- c) In a fibrosed area
- d) In scar tissue
- e) In a limb following removal of a draining lymph node

Ans : a) T b) T c) F d) F e) T

**Q. Oedema is caused by (BIRDEM-04)**

- |  |   |
|--|---|
| a) Increased hydrostatic pressure in venule  | T   |
| b) Increased plasma colloid osmotic pressure | F   |
| c) Lymphatic obstruction                     | T   |
| d) Essential hypertension                    | F   |
| e) Hyper-aldosteronism                       | T (because Na and H <sub>2</sub> O retention) |

**Q. Localized oedema occurs in- (BSMMU-MS-04Ja)**

- |                          |                             |
|--------------------------|-----------------------------|
| a) Allergic reactions    | T                           |
| b) Venous obstruction    | T                           |
| c) Nephrotic syndrome    | F (because anasarca occurs) |
| d) Lymphatic obstruction | T                           |
| e) Cardiac failure       | F (because anasarca occurs) |

**Q. Angioneurotic oedema is associated with (M. phil, Diploma (DMC) – 03, July)**

- |                          |   |
|--------------------------|---|
| a) depression            | F   |
| b) complement deficiency | F   |
| c) IgE                   | T (also associated with type 1 hypersensitivity reaction) |
| d) asthma                | F   |
| e) NSAID poisoning       | F   |

**Help link:** Deficiency of C1 esterase inhibitor leads to development of Hereditary angioneurotic oedema.  
C1 esterase is a complement inhibitory substance.

**Q. A high protein content is characteristic of the edema fluid associated with: (MD/MS (DMC)-02Ja)**

- |                               |  |
|-------------------------------|--|
| A. Acute inflammation         | T  |
| B. Allergic edema             | T  |
| C. Cardiac failure            | F  |
| D. Famine (nutritional edema) | F  |
| E. The nephrotic syndrome     | F ( <i>massive proteinuria leads to decrease proteinemia</i> ) |

## Hyperemia & Congestion

**Hyperemia** is an *active process* in which arteriolar dilation (e.g., at sites of inflammation or in skeletal muscle during exercise) leads to increased blood flow. Affected tissues turn red (*erythema*) because of the engorgement of vessels with oxygenated blood.

**(Ref: Robbins & Cotrans-9<sup>th</sup>, P-115)**

**Congestion** is a *passive process* resulting from reduced outflow of blood from a tissue. It can be systemic, as in cardiac failure, or local, as in isolated venous obstruction. Congested tissues take on a dusky reddish-blue color (*cyanosis*) due to red cell stasis and the accumulation of deoxygenated hemoglobin.

**(Ref: Robbins & Cotrans-9<sup>th</sup>, P-115)**

**Congestion** is a *passive process* resulting from reduced outflow of blood from a tissue.

**Example:** It can be systemic, as in cardiac failure, or local, as in isolated venous obstruction.

**Etiology of congestion:**

**A. Systemic congestion:** CCF-

- LVF- congestion in lung
- RVF- congestion in the entire body except lungs.

**B. Localized congestion:** Impaired venous return from a localized area e.g. leg, intestine.

**Effects of congestion:**

1. Congested tissues take on a dusky reddish-blue color (*cyanosis*) due to red cell stasis and the accumulation of deoxygenated hemoglobin.
2. As a result of the increased volumes and pressures, congestion commonly leads to edema.
3. In long-standing *chronic passive congestion*, the lack of blood flow causes chronic hypoxia, potentially resulting in ischemic tissue injury and scarring.
4. Capillary rupture in chronic congestion can also cause small hemorrhagic foci; subsequent catabolism of extravasated red cells can leave residual telltale clusters of hemosiderin-laden macrophages.

**(Ref: Robbins & Cotrans-9<sup>th</sup>, P-115)**

**Morphology:**

**Gross:** The cut surfaces of congested tissues are often discolored due to the presence of high levels of poorly oxygenated blood.

**Microscopically,**

**Lungs:**

a) **Acute pulmonary congestion** – It exhibits

- engorged alveolar capillaries
- alveolar septal edema
- focal intra-alveolar hemorrhage.

b) **Chronic pulmonary congestion** –

- the septa are thickened and fibrotic.
- the alveoli often contain numerous hemosiderin-laden macrophages called **heart failure cells**.

**Liver**

a) **Acute hepatic congestion:**

- central vein and sinusoids are distended.
- centrilobular hepatocytes can be frankly ischemic while the periportal hepatocytes—better oxygenated because of proximity to hepatic arterioles—may only develop fatty change.

b) **Chronic passive hepatic congestion:**

- centrilobular regions are grossly red-brown and slightly depressed (because of cell death) and are accentuated against the surrounding zones of uncongested tan liver (**nutmeg liver**).
- Microscopically, there is centrilobular hemorrhage, hemosiderin-laden macrophages, and degeneration of hepatocytes.

(Ref: Robbins & Cotrans-9<sup>th</sup>, P-116)

**Kidneys:**

In long standing chronic congestion, the spleen progressively enlarges and may up to 500-700 gms. Fibrous thickening and haemosiderin deposits within the oedematous congested sinusoidal walls produce the characteristic pattern of congestive splenomegaly.

**Difference between hyperemia & congestion:**

Traits	Hyperemia	Congestion
<b>1. Definition</b>	<i>Hyperemia</i> is an active process in which arteriolar dilation (e.g., at sites of inflammation or in skeletal muscle during exercise) leads to increased blood flow.	<i>Congestion</i> is a passive process resulting from reduced outflow of blood from a tissue.
<b>2. Active or passive process</b>	1. Active process	Passive process.
<b>3. Cause</b>	2. It is produced by arteriolar dilatation.	It results from impaired venous drainage.
<b>4. Effect</b>	3. Increased blood flow.	Reduced outflow of blood from a tissue.
<b>5. Morphology</b>	4. It causes increase redness of the affected part ( <i>erythema</i> )	It causes increased reddish-blue coloration in affected part ( <i>cyanosis</i> )
<b>6. Capillary bed</b>	Engorged with oxygenated blood	Swollen with deoxygenated venous blood
<b>7. Example</b>	5. It is seen in febrile condition, muscular exercise & inflammation.	It occurs either systemic process (e.g. CCF) or localized process (e.g. venous return of blood from an extremity is obstructed).

(Ref: Robbins & Cotrans-9<sup>th</sup>, P-115-116)

**Q. 'Heart failure cells' in chronic pulmonary congestion is/are (BSMMU-Residency - MD/MS, Basic science,**

**Paediatrics – March '19)**

- a) carbon laden histiocytes
- b) hemosiderin laden histiocytes
- c) cardiac myocytes
- d) lipofuscin loaded histiocytes
- e) pneumocytes

Ans. a) F b) T c) F d) F e) F

**Help Link:**

**Chronic pulmonary Congestion:** caused by CCF, septa thickened and fibrotic, alveoli contains Hemosiderin laden macrophage / heart failure cells.(basic mechanisms of brown induration of lung)

**Q. Acute pulmonary congestion is characterized by (BSMMU – Non-Residency – MD, MS, Basic science – July' 18)**

- a) engorged alveolar capillaries
- b) alveolar septal edema
- c) focal intra-alveolar hemorrhage
- d) fibrotic thick alveolar septa
- e) hemosiderin-laden macrophages in alveolar spaces

Ans. a) T b) T c) T d) F e) F

**Q. Vascular congestion may lead to (BSMMU – Residency – MD, MS, Basic Science – March' 18/ March' 15)**

- a) brown indurations of lung
- b) brown atrophy of heart
- c) nutmeg liver
- d) chocolate cyst in ovary
- e) anasarca

Ans. a) T b) F c) T d) F e) F

**Q. Pathologic conditions caused by vascular congestion are: (BSMMU – MD – January, 2010)**

- |                             |   |
|-----------------------------|---|
| a) nutmeg liver             | T |
| b) brown induration of lung | T |
| c) strawberry gallbladder   | F |
| d) stasis dermatitis of leg | F |
| e) chocolate cyst of ovary  | F |

(Ref: Robbins-9<sup>th</sup>, P-116)

## Hemostasis

### Process of hemostasis

- Immediately arteriolar vasoconstriction
- Primary hemostasis: formation of platelet plug
- Secondary hemostasis: deposition of fibrin
- Clot stabilization and resorption.

### Platelet:

- Disc shaped, anucleate
- Derived from megakaryocytes from bone marrow
- Functions depends upon glucoprotein receptor, contractile cytoskeleton, and two types cytoplasmic granules
- **Granules:**
  - 1. **alpha granules-**
    - have p-selectin on membrane,
    - fibrinogen,
    - factor V,
    - vWF, fibronectin,
    - platelet factor 4,
    - PDGF,
    - TGF-beta
  - 2. **Delta granules-**
    - ADP, ATP, Ca+, serotonin, epinephrine

**Why blood does not clot in inside the blood vessels?**

- **Platelet inhibitory factors:** intact endothelium, endothelium release- PGI<sub>2</sub>, NO, ADP, endothelial cells bind to thrombin.
- **Anticoagulant effect:** thrombomodulin, endothelial protein C receptor, heparin like molecules, TF pathway inhibitor, cofactor protein S, t-PA.

## THROMBUS

**Thrombosis:** It is the process of formation of a solid mass in the circulation from the constituents of streaming blood.

(Ref: Walter & Israel)

**Thrombus:** It is a solid or semi-solid mass in the circulation from the constituents of streaming blood.

### ■ Different types of thrombus:

#### A. Based on site:

##### 1. Arterial thrombus:

- a) Thrombus on ulcerated atheromatous plaque - in coronary arteries
- b) On atheroma of abdominal aorta
- c) Thrombus in thromboangiitis obliterans (Buerger's disease)
- d) Laminated thrombus - in aneurism
- e) Trauma

##### 2. Venous thrombus:

- a) Phlebothrombosis
- b) Thrombophlebitis
- c) Other types — thrombophlebitis migrans, iliofemoral thrombosis

##### 3. Thrombosis in the heart:

- a) Vegetations (e.g. infective endocarditis)
- b) Mural thrombus
- c) Laminated thrombus (in aneurism of heart)
- d) Ball thrombus

#### C. Based on occlusion of lumen:

1. Occlusive thrombus — Completely occludes the lumen
2. Mural thrombus — It is attached to the wall but does not completely occlude the lumen

#### B. Based on presence of infection:

1. Bland / aseptic thrombus
2. Septic / infected thrombus.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-125,126; Prof. Khaleque)

### ■ Fates of the thrombus:

1. **Propagation:** Thrombi accumulate additional platelets and fibrin.
2. **Embolization:** Thrombi dislodge and travel to other sites in the vasculature.
3. **Dissolution:** Dissolution is the result of fibrinolysis, which can lead to the rapid shrinkage and total disappearance of recent thrombi. In contrast, the extensive fibrin deposition and crosslinking in older thrombi renders them more resistant to lysis. This distinction explains why therapeutic administration of fibrinolytic agents such as t-PA (e.g., in the setting of acute coronary thrombosis) is generally effective only when given in the first few hours of a thrombotic episode.

**4. Organization & recanalization:** Older thrombi become organized by the ingrowth of endothelial cells, smooth muscle cells, and fibroblasts. Capillary channels eventually form that re-establish the continuity of the original lumen, albeit to a variable degree.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-125-126)

**Differences between clot & thrombus:**

Traits	Clot	Thrombus
1. Composition	A solid mass of fibrin. No platelet scaffold	A solid mass of platelets and fibrin. Platelet scaffold is present
2. Where found	In living body or in a test tube	Only in living body
3. Flow of blood	Formed in a column of static blood	Formed in streaming blood
4. Friability	Friable	Not very friable
5. Attachment to wall	Easily detachable from the wall	Firmly attached to the wall
6. Line of Zahn	Absent	Present

(Ref: Prof. Khakque/43)

Thrombi occurring in heart chambers or in the aortic lumen are designated **mural thrombi**. Abnormal myocardial contraction (arrhythmias, dilated cardiomyopathy, or myocardial infarction) or endomyocardial injury (myocarditis or catheter trauma) promotes cardiac mural thrombi, while ulcerated atherosclerotic plaque and aneurysmal dilation are the precursors of aortic thrombi.

**Arterial thrombi** are frequently occlusive; the most common sites in decreasing order of frequency are the coronary, cerebral, and femoral arteries. They typically consist of a friable meshwork of platelets, fibrin, red cells, and degenerating leukocytes. Although these are usually superimposed on a ruptured atherosclerotic plaque, other vascular injuries (vasculitis, trauma) may be the underlying cause.

**Venous thrombosis (phlebothrombosis)** is almost invariably occlusive, with the thrombus forming a long luminal cast. They tend to contain more enmeshed red cells (and relatively few platelets) and are therefore known as red, or stasis, thrombi. Venous thrombi are firm, are focally attached to the vessel wall, and contain lines of Zahn, features that help distinguish them from postmortem clots (see later). The veins of the lower extremities are most commonly involved (90% of cases); however, upper extremities, periprostatic plexus, or the ovarian and periuterine veins can also develop venous thrombi. Under special circumstances, they can also occur in the dural sinuses, portal vein, or hepatic vein.

**Postmortem clots** can sometimes be mistaken for antemortem venous thrombi. However, clots that form after death are gelatinous and have a dark red dependent portion where red cells have settled by gravity and a yellow "chicken fat" upper portion, and are usually not attached to the underlying vessel wall.

Thrombi on heart valves are called **vegetations**. Blood borne bacteria or fungi can adhere to previously damaged valves (e.g., due to rheumatic heart disease) or can directly cause valve damage; in either case, endothelial injury and disturbed blood flow can induce the formation of large thrombotic masses (**infective endocarditis**). Sterile vegetations can also develop on noninfected valves in persons with hypercoagulable states, so-called **nonbacterial thrombotic endocarditis**. Less commonly, sterile verrucous endocarditis (**Libman-Sacks endocarditis**) can occur in the setting of systemic lupus erythematosus.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-125)

**Question Bank**

**Q. In venous thrombosis, thrombi are (BSMMU – Residency - MD/MS, Basic science, Paediatrics – March 19)**

- a) almost occlusive
- b) rich in platelets
- c) common in periprostatic plexus
- d) attached to the vessel wall
- e) devoid of lines of Zahn

Ans. a) T b) F c) T d) T e) F

**Table 4.6****Distinguishing features of arterial and venous thrombi.**

FEATURE	ARTERIAL THROMBI	VENOUS THROMBI
1. Blood flow	Formed in rapidly-flowing blood of arteries and heart	Formed in slow-moving blood in veins
2. Sites	Common in aorta, coronary, cerebral, iliac, femoral, renal and mesenteric arteries	Common in superficial varicose veins, deep leg veins, popliteal, femoral and iliac veins
3. Thrombogenesis	Formed following endothelial cell injury e.g. in atherosclerosis	Formed following venous stasis e.g. in abdominal operations, child-birth
4. Development	Usually mural, not occluding the lumen completely, may propagate	Usually occlusive, take the cast of the vessel in which formed, may propagate in both directions
5. Macroscopy	Grey-white, friable with lines of Zahn on surface	Red-blue with fibrin strands and lines of Zahn
6. Microscopy	Distinct lines of Zahn composed of platelets, fibrin with entangled red and white blood cells	Lines of Zahn with more abundant red cells
7. Effects	Ischaemia leading to infarcts e.g. in the heart, brain etc	Thromboembolism, oedema, skin ulcers, poor wound healing

(Ref. Harsh Mohan pathology-7<sup>th</sup>, P-103)

**Q. Factors possessing high risk for thrombogenesis are (BSMMU – Non-Residency – MD, MS, Basic science – July '18)**

- a) smoking
- b) cancer
- c) prosthetic heart valves
- d) oral contraceptives
- e) sickle cell anemia

Ans. a) F b) T c) T d) F e) F

(Ref. Robbins-9<sup>th</sup>, P-123)

**Q. Conditions predisposing to thrombosis are (BSMMU – Diploma - Dentistry – July '18)**

- a) iron deficiency anemia
- b) atrial fibrillation
- c) prolonged bed rest
- d) disseminated cancer
- e) aplastic anemia

Ans. a) F (Hyperviscosity syndrome such as Polycythaemia vera, Sickle cell anaemia causes impede blood flow causing stasis followed by thrombosis) b) T c) T d) T e) F

**Q. Abnormalities that lead to thrombosis are (BSMMU – Residency - MD, MS, Basic Science, Dentistry - March '17)**

- a) endothelial damage
- b) hypercholesterolemia
- c) thrombocytopenia
- d) antithrombin III deficiency
- e) over expression of protein C

Ans. a) T b) T c) F d) T e) F

**HELP LINK:****Causes of thrombosis/ pathogenesis:**

Three primary abnormalities that lead to thrombus formation (called Virchow's triad):

- (1) endothelial injury,
- (2) stasis or turbulent blood flow, and
- (3) hypercoagulability of the blood.

Three primary influences are involved in thrombus formation, which is called **Virchow's triad**:

**Fig: Virchow's triad**

1. **Endothelial Injury:** It is particularly important in thrombus formation in the heart or the arterial circulation. e.g.

- after endocardial injury due to myocardial infarction
- over ulcerated plaques in atherosclerotic arteries
- at sites of traumatic or inflammatory vascular injury (*vasculitis*)

**Process:** Endothelial damage → exposure of subendothelial collagen, adhesion of platelets, release of tissue factor and local depletion of prostacyclin (PGI<sub>2</sub>) and plasminogen activators. The end result is formation of a permanent plug and thrombus.

Endothelial dysfunction can be induced by a wide variety of insults, including hypertension, turbulent blood flow, bacterial endotoxins, radiation injury, metabolic abnormalities such as homocystinemia or hypercholesterolemia, and toxins absorbed from cigarette smoke.

2. **Alterations in Normal Blood Flow:**

**Turbulence** contributes to arterial and cardiac thrombosis by causing endothelial injury or dysfunction, as well as by forming countercurrents and local pockets of stasis.

**Stasis** is a major contributor in the development of venous thrombi.

**Process:** Stasis and turbulence therefore:

- Promote endothelial activation, enhancing procoagulant activity, leukocyte adhesion, etc., in part through flow-induced changes in endothelial cell gene expression.
- Disrupt laminar flow and bring platelets into contact with the endothelium
- Prevent washout and dilution of activated clotting factors by fresh flowing blood and the inflow of clotting factor inhibitors

Turbulence and stasis contribute to thrombosis in several clinical settings:

- Ulcerated atherosclerotic plaques.
- Aortic and arterial dilations called *aneurysms*
- Acute myocardial infarctions
- Rheumatic mitral valve stenosis
- Hyperviscosity (such as is seen with polycythemia vera)
- Sickle cell anemia

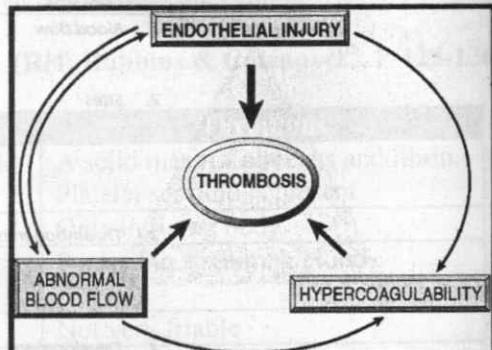
3. **Hypercoagulability:** It is loosely defined as any alteration of the coagulation pathways that predisposes to thrombosis.

Hypercoagulability can be divided as follows:

**Hypercoagulable States:**

A. Primary (Genetic)

**Common**



(Ref: Prof. Knobbe/43)

- Factor V mutation (Arg to Glu substitution in amino acid residue 506, leading to resistance to activated protein C; factor V Leiden)
- Prothrombin mutation (G20210A noncoding sequence variant leading to increased prothrombin levels)
- Increased levels of factors VIII, IX, XI, or fibrinogen (genetics unknown)

**Rare**

- Antithrombin III deficiency
- Protein C deficiency
- Protein S deficiency

**Very Rare**

- Fibrinolysis defects
- Homozygous homocystinuria (deficiency of cystathione  $\beta$ -synthetase)

**B. Secondary (Acquired)****High Risk for Thrombosis**

- Prolonged bed rest or immobilization
- Myocardial infarction
- Atrial fibrillation
- Tissue injury (surgery, fracture, burn)
- Cancer
- Prosthetic cardiac valves
- Disseminated intravascular coagulation
- Heparin-induced thrombocytopenia
- Antiphospholipid antibody syndrome

**Lower Risk for Thrombosis**

- Cardiomyopathy
- Nephrotic syndrome
- Hyperestrogenic states (pregnancy and postpartum)
- Oral contraceptive use
- Sickle cell anemia
- Smoking

(Ref: Robbins & Cotran-9<sup>th</sup>, P-123)**Q. Secondary causes of hypercoagulability are (BSMMU – Non-Residency – MD, MS, Paediatrics, Basic Science – July' 19)**

- cancer
- antiphospholipid antibody syndrome
- factor V mutation
- antithrombin III deficiency
- myocardial infarction

Ans. a) T b) T c) F (primary) d) F (Primary) e) T

(Ref: Robbins-9<sup>th</sup>, P-123)**Q. High risk conditions for thrombosis are (BSMMU – Residency - Dentistry - March' 17)**

- prolonged bed rest
- prosthetic heart valve
- nephrotic syndrome
- hyperestrogenic state
- cancers

Ans. a) T b) T c) F d) F e) T

**Q. In venous thrombosis, the thrombi (BSMMU – Non-Residency – MD, MS, Basic science, Dentistry – July' 16)**

- |  |   |
|--|---|
| a) are almost occlusive                | T |
| b) contain more RBC                    | T |
| c) are firm                            | T |
| d) are not attached to the vessel wall | F |
| e) do not contain lines of Zahn        | F |

**Help link:**

**Difference between arterial and venous thrombi:**

<b>Arterial thrombi</b>	<b>Venous thrombosis(phlebothrombosis)</b>
Frequently occlusive/ friable	Invariably occlusive/ not friable
Most common site: coronary, cerebral, femoral artery	Sites: veins of the lower extremity(90% cases), upper extremity, periprostatic plexus, ovarian and periuterine veins, dural sinuses, portal vein, hepatic vein
Composed of friable meshwork of platelets, fibrin, RBC, degenerating leukocytes	Enmeshed RBC, few platelets, (known as stasis or red thrombi)
Cause: <ul style="list-style-type: none"> <li>• due to endothelial injury and turbulence</li> <li>• on a ruptured atherosclerotic plaque, vasculitis, trauma</li> </ul>	Cause: due to stasis
Retrograde flow	Flowing along the direction of blood/ along luminal cast, sluggish venous circulation.
Frequently embolize	Firm, focally attached to the vessel wall
Firmly attached to the wall	Loosely attached to the wall
	Contains lines of Zahn(differentiate from postmortem clot)

**Q. Following are the fates of a thrombus: (BSMMU – M. Phil, Diploma (Non-Residency)–March-2012, DMC & others – MD/MS – March-2012)**

- |                     |   |
|---------------------|---|
| a) dissolution      | T |
| b) keloid formation | F |
| c) neoplasia        | F |
| d) scar formation   | F |
| e) embolization     | T |

**Q. Following are the fate of a thrombus (BSMMU – MD/MS (Residency) – January, 2011)**

- |                            |   |
|----------------------------|---|
| a) resolution/ dissolution | T |
| b) embolization            | T |
| c) atherosclerosis         | F |
| d) keloid formation        | F |
| e) recanalization          | T |

**Q. Cardiac mural thrombi arise from (BSMMU – MD/MS (Residency) – January, 2011)**

- |                                  |   |
|----------------------------------|---|
| a) ulcerated atheromatous plaque | F |
| b) cardiac arrhythmias           | T |
| c) myocardial infarction         | T |
| d) dilated cardiomyopathy        | T |
| e) aortic aneurysm               | F |

**Help link:**

**Mural thrombus:** Thrombi occurring in heart chambers or in the aortic lumen are designated **mural thrombi**. or, It is a partial thrombus which is attached to a wall of the capacious lumina of the vascular channels.

**■ Sites & causes of formation:**

1. **Cardiac mural thrombi:** due to

- Abnormal myocardial contraction (arrhythmias, dilated cardiomyopathy, or myocardial infarction)
- endomyocardial injury (myocarditis or catheter trauma)

2. **Aortic mural thrombi:** due to

- ulcerated atherosclerotic plaque
- Aneurysmal dilatation.

**■ Appearance:** The thrombi have apparent laminations called **lines of Zahn**; these represent pale platelet and fibrin deposits alternating with darker red cell-rich layers.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-125)

**Q. Virchow's triad of thrombosis includes:** (BSMMU - M. Phil, Diploma – July '10)

- |                                       |   |
|---------------------------------------|---|
| a) Hypercoagulability                 | T |
| b) Endothelial injury                 | T |
| c) Generation of plasmin              | F |
| d) Activation of antithrombin III     | F |
| e) Stasis of turbulence of blood flow | T |

**Q. Causes of superficial thrombophlebitis includes** (MD/MS (DMC)-08Ja)

- |                              |   |
|------------------------------|---|
| a) stasis                    | F |
| b) intra-venous infusion     | F |
| c) insect bite               | F |
| d) trauma                    | T |
| e) intra abdominal infection | T |

#### HELP LINK:

**Thrombophlebitis:** Inflammation in a vein causes damage to endothelial cells and on this platelets are deposited.

#### Causes:

1. **Bacterial inflammation**, e.g. in appendicular veins in acute appendicitis and in infected haemorrhoids. It may release infected emboli, i.e. pyaemia (e.g. portal pyaemia):
2. **Sterile inflammation**, e.g. due to direct trauma, ionizing radiation.
3. Varicose vein
4. Intravenous cannulation
5. Previous venous diseases
6. Abnormalities of blood coagulation factors
7. Buerger's disease

Traits	Phlebothrombosis	Thrombophlebitis
<b>1. Definition</b>	Thrombosis in veins having no inflammation	Thrombosis in an inflamed vein
<b>2. Site</b>	Usually calf veins	Anywhere
<b>3. Clinical picture</b>	Silent, few signs or symptoms	Pain & signs of acute inflammation obvious.
<b>4. Major cause</b>	Stasis	Inflammation of vein wall.
<b>5. Size of primary thrombus</b>	Small	Larger
<b>6. Size of propagated thrombus</b>	Large, poorly anchored	None or short & well anchored
<b>7. Emboli</b>	Sterile, common & massive	Rare-pyaemic

**Q. Factors increasing risk for thrombus formation include:** (BSMMU - M. Phil, Diploma, July-09)

- |                   |   |
|-------------------|---|
| a) Protein C      | F |
| b) Protein S      | F |
| c) Cancer         | T |
| d) Immobilization | T |
| e) Cardiomyopathy | T |

#### HELP LINK:

Natural blood clotting inhibitors are Anti-thrombin III, Protein C, protein S.

**Q. Embolism is a sequel to:** (BSMMU - M. Phil, Diploma, July-08)

- |                                   |   |
|-----------------------------------|---|
| a) pelvic vein thrombosis         | T |
| b) fracture of long bones         | T |
| c) mitral stenosis                | T |
| d) essential hypertension         | T |
| e) administration of Progestogens | F |

**Q. A thrombus is formed:** (BSMMU – MD/MS - January, 2008)

- |                            |   |
|----------------------------|---|
| a) commonly in arteries    | F |
| b) even in cardiac chamber | T |
| c) in flowing blood        | T |
| d) in hypoxia              | F |
| e) both within and system  | F |

**Q. A venous thrombus -** (BSMMU - M. Phil, Diploma, July-07)

- |   |   |
|---|---|
| a) Is dark red in colour                    | T |
| b) Can not propagate                        | F |
| c) Is common than arterial thrombi          | T |
| d) Commonly gives rise to cerebral embolism | F |
| e) Contains prominent lines of Zahn         | T |

**HELP LINK:**

- Venous thrombosis contains more enmeshed erythrocytes, so known as **red or stasis thrombi**.
- Venous thrombosis most commonly affects the veins of the lower extremities (90% cases). Less commonly, venous thrombi may develop in the upper extremities, periprostatic plexus or the ovarian and periuterine veins, under special circumstances, they may be found in the dural sinuses, the portal vein, or the hepatic vein.
- When formed in the heart or aorta, thrombi may have grossly (and microscopically) apparent laminations, called **lines of zahn**; these are produced by alternating pale layers of platelets admixed with some fibrin and darker layers containing more red cells. Lines of zahn are significant only in that they imply thrombosis at a site of blood flow; in veins or in smaller arteries, the laminations are typically not as apparent, and in fact thrombi formed in the sluggish flow of venous blood usually resemble statically coagulated blood.

**Q. Phlebothrombosis-** (BSMMU-MD/MS-07Ja)

- |  |   |
|--|---|
| a) Refers to venous thrombosis                         | T |
| b) Refers to inflammation of vein wall                 | F |
| c) Commonly starts in the deep calf veins              | T |
| d) Is mainly due to stasis of blood                    | T |
| e) Shows signs of acute inflammation at overlying skin | F |

**Q. Thrombus in a vein -** (BSMMU-MD/MS-06Ja)

- A. are usually red
- B. contains more platelets than arteriolar thrombus
- C. break easily to give rise to embolus
- D. are never occlusive
- E. are formed due to stasis

Ans.

- a) T                            b) F (*Contains more enmeshed erythrocytes, so red*)  
 c) F (*rarely embolize*)    d) F (*It is almost invariably occlusive*)  
 e) T

**Q. Formation of thrombus-** (BSMMU – MD/MS - 05Ja)

- A. is seen frequently in rapidly flowing blood
- B. is dependent on platelet content of blood
- C. can be clinically silent
- D. sometimes occurs in cardiac chambers
- E. can be prevented by reducing platelet adhesion

Ans.

- a) T (*Both stasis & turbulence may cause thrombosis*)  
 b) T (*↑Platelets → ↑coagulability of blood → ↑Thrombogenesis*) c) T    d) T    e) T

**Q. Endothelial injury promotes thrombosis in - (MD/MS (DMC)-04Ja)**

- |                                  |   |
|----------------------------------|---|
| a) Anti-thrombin III deficiency  | F |
| b) Myocardial infarction         | T |
| c) Homocysteinemia               | T |
| d) Ulcerated atheromatous plaque | T |
| e) Protein C deficiency          | F |

**Q. A thrombus may results in- (BIRDEM-04)**

- |                                |   |
|--------------------------------|---|
| a) Neoplastic transformation   | F |
| b) Embolization                | T |
| c) Retraction & recanalization | T |
| d) Abscess formation           | F |
| e) Organization.               | T |

**Q. The following statements can be made about thrombosis - (BSMMU-MD/MS-03Ja)**

- |  |                                      |
|--|--------------------------------------|
| a) Thrombi are always formed in the streaming blood        | F                                    |
| b) They are formed from the constituents of blood          | T                                    |
| c) Pale thrombus is the most common type of thrombus       | F (venous or red thrombus is common) |
| d) An increase in the prostacyclin level is a risk factor. | F                                    |
| e) Coralline thrombus is mixed thrombus.                   | T                                    |

**Q. Thrombus formation is favoured by: (MD/MS (DMC)-02Ja)**

- |                                   |  |
|-----------------------------------|--|
| A. Damage to vascular endothelium | T  |
| B. Slowing of blood flow          | T  |
| C. Increased platelet count       | T  |
| D. Heparin Therapy                | F  |
| E. Estrogen therapy               | T (Composition of OCP lower the risk of hypercoagulable state) |

**Q. A thrombus may results in- (BIRDEM-04)**

- |                                |   |
|--------------------------------|---|
| a) Neoplastic transformation   | F |
| b) Embolization                | T |
| c) Retraction & recanalization | T |
| d) Abscess formation           | F |
| e) Organization.               | T |

**HELP LINK:****Fate of thrombus:**

1. Propagation
2. Embolization
3. Dissolution
4. Organization & recanalization

**N.B.** • Unfractionated heparin may cause thrombus formation. • Low molecular wt. heparin – no thrombus

**Q. A pale thrombus - (BSMMU-MS-01Ja)**

- |                                |
|--------------------------------|
| a) Is rich in cholesterol      |
| b) Is seen in arteries         |
| c) Commonly embolizes          |
| d) Contains less RBC           |
| e) Is common than red thrombus |
- Ans. a) T b) T  
c) T (because more friable) d) T e) F

**Help link:**

- Atherosclerotic plaque is a good example of pale thrombus, white-yellow in colour. S
- Superimposed thrombus over ulcerated plaque is red brown. Site: Lower abdominal aorta, coronary artery, popliteal artery, ICA, vessels of circle of Willis.

## Heparin induced thrombocytopenia

### Heparin induced thrombocytopenia:

- Unfractionated heparin, induce Ab that recognizes the complexes of heparin and platelet factor 4, leads to activation, aggregation and consumption of platelet(leads to thrombocytopenia)
- This is due to platelet and endothelial damage by Ab.
- Low molecular weight heparin (enoxaparin): HIT occurs less frequently due to directly inhibit the factor X and thrombin.

## Anti-phospholipid antibody syndrome

### Anti-phospholipid antibody syndrome:

- Previously celled lupus anticoagulant syndrome
- Features:
  - ✓ recurrent thromboses,
  - ✓ repeated miscarriages,
  - ✓ cardiac valve vegetations,
  - ✓ thrombocytopenia,
  - ✓ pulmonary embolism, pul. HTN,
  - ✓ Stroke, bowel infarction, renovascular HTN,
  - ✓ fetal loss (not due to thrombosis but Ab prevents the growth and differentiation of trophoblast),
  - ✓ renal microangiopathy leads to RF.
- Types:
  - Primary-**
    - ✓ hypercoagulable states,
    - ✓ no autoimmune disease assoc.
    - ✓ cause-exposure to certain drugs and infections
  - Secondary-**
    - ✓ associated with autoimmune disease (SLE), hence the name lupus anticoagulant.
    - ✓ **Treatment:** anticoagulant, immunosuppression.

## DIC (disseminated intravascular coagulation)

### DIC (disseminated intravascular coagulation):

- Synonyms: consumption coagulopathy, defibrillation syndrome
- Acquired disorder
- Widespread systemic activation of coagulation with microthrombi
- Bleeding diathesis due to depletion of coagulation factors and platelet.

### ■ Causes of DIC or Disseminated Intravascular Coagulation:

1. Infection/ sepsis: by
  - E Coli
  - Streptococcus pneumonia
  - Neisseria meningitidis
  - Malaria
2. Trauma
3. Obstetric:
  - Amniotic fluid embolism
  - Placental abruption
  - Pre-eclampsia
4. Severe liver failure
5. Malignancy: solid tumours and leukaemia

6. Tissue destruction: pancreatitis, burns
7. Vascular abnormalities: vascular aneurysm, liver haemangiomas
8. Toxic/ immunological: ABO incompatibility, snake bites, recreational drugs

(Ref: Davidson-22<sup>nd</sup>, P-1056)

### ■ Investigations:

- **Platelet count:** Thrombocytopenia,
- **PT** (Prothrombin time): prolonged (due to factor V and fibrinogen deficiency)
- **APTT** (Activated partial thromboplastin time): prolonged (due to factor V, VIII, and fibrinogen deficiency)
- **Fibrinogen** concentration: low
- **FDPs** (fibrinogen degradation products): increased

(Ref: Davidson-22<sup>nd</sup>, P-1055)

ISTH scoring system for diagnosis of DIC	
Presence of an associated disorder	Essential
Platelets	> 100 = 0 < 100 = 1 < 50 = 2
Elevated fibrin degradation products	No increase = 0 Moderate = 2 Strong = 3
Prolonged prothrombin time	< 3 sec = 0 > 3 sec but < 6 sec = 1 > 6 sec = 2
Fibrinogen	> 1 g/L = 0 < 1 g/L = 1
Total score	
$\geq 5$ = Compatible with overt DIC	
$< 5$ = Repeat monitoring over 1–2 days	

(ISTH = International Society for Thrombosis and Haemostasis)

(Ref: Davidson-22<sup>nd</sup>, P-1056)

## Embolism

■ **Embolism:** Formation of emboli is called embolism.

■ **Embolus:** An embolus is a detached intravascular solid, liquid, or gaseous mass that is carried by the blood from its point of origin to a distant site, where it often causes tissue dysfunction or infarction.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-127)

Virtually 99% of all emboli represent some part of dislodged thrombus, hence the commonly used term thromboembolism.

### ■ Classification of embolism:

#### A. On the basis of aetiology/ Causes of embolism:

##### 1. Solid:

- Thromboemboli (99%) (*pulmonary or systemic*)
- Droplets of fat (*occurs in bone fracture*)
- Atherosclerotic debris (*cholesterol emboli*)
- Tumor fragments
- Bits of bone marrow
- Foreign bodies eg. bullets
- Parasites

##### 2. Liquid: Amniotic fluid

##### 3. Gaseous: Bubbles of air or N<sub>2</sub>

(Ref: Robbins & Cotran-9<sup>th</sup>, P-127)

#### B. According to location:

1. Arterial embolism
2. Venous embolism
3. Lymphatic embolism

**Q. Sources of systemic emboli are:** (BSMMU– M. Phil, Diploma (Non-Residency)–11Ju, DMC & others – MD/MS – 11Ju)

- |  |                            |
|--|----------------------------|
| a) deep veins of lower extremities                   | F (80% from intra-cardiac) |
| b) left ventricle secondary to myocardial infarction | T                          |
| c) atria due to rheumatic heart disease              | T                          |
| d) some cases of cardiomyopathy                      | T                          |
| e) cerebral aneurysm                                 | F                          |

#### HELP LINK:

**Systemic Thromboembolism:** Most systemic emboli (80%) arise from intracardiac mural thrombi, two thirds of which are associated with left ventricular wall infarcts and another one fourth with left atrial dilation and fibrillation. The remainder originates from aortic aneurysms, atherosclerotic plaques, valvular vegetations, or venous thrombi (paradoxical emboli); 10% to 15% are of unknown origin. In contrast to venous emboli, the vast majority of which lodge in the lung, arterial emboli can travel to a wide variety of sites; the point of arrest depends on the source and the relative amount of blood flow that downstream tissues receive. Most come to rest in the lower extremities (75%) or the brain (10%), but other tissues, including the intestines, kidneys, spleen, and upper extremities, may be involved on occasion. The consequences of systemic emboli depend on the vulnerability of the affected tissues to ischemia, the caliber of the occluded vessel, and whether a collateral blood supply exists; in general, however, the outcome is tissue infarction.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-127-128)

## Pulmonary embolism

**Q. Consequences of pulmonary embolism are** (BSMMU –Residency - MD/MS, Basic science, Paediatrics – March' 19)

- a) sudden death
- b) neurological symptom
- c) disseminated intravascular coagulation
- d) pulmonary hypertension
- e) cor pulmonale

Ans. a) T b) F c) F d) T e) T

#### Pulmonary embolism:

- Source: 95% from Leg DVT
- Effects:
  - In 60-80% cases: are clinically silent bcoz they are small, organized
  - Obstruction in 60% of cases:
    - sudden death,
    - rt heart failure/ Corpulmonale,
    - cardiovascular collapse
  - Obstruction to medium sized arteries:
    - vessels rupture,
    - Hge occurs but no pulmonary infarction occurs due to dual blood supply.
  - If bronchial artery obstruct causes
    - LVF and
    - Infarction
  - Obstruction in small end artery: causes Hge and infarction
  - Multiple emboli: leads to Pul HTN, Right ventricular failure

(Ref: Robbins-9<sup>th</sup>, P-127)

**Q. The facts about pulmonary thromboembolism are:** (BSMMU – MS - January, 2010)

- |   |   |
|---|---|
| a) most originate from deep veins of leg  | T |
| b) they are invariably symptomatic        | F |
| c) can cause sudden cardiac death         | T |
| d) are frequent cause of pleural effusion | F |
| e) can lead to pulmonary hypertension     | T |

**HELP LINK:**

■ **Pulmonary embolism:** In more than 95% of cases, pulmonary embolisms originate from leg deep vein thromboses (DVTs). Fragmented thrombi from DVTs are carried through progressively larger channels and the right side of the heart before slamming into the pulmonary arterial vasculature.



Depending on the size of the embolus, it can occlude the main pulmonary artery, straddle the pulmonary artery bifurcation (*saddle embolus*), or pass out into the smaller, branching arteries.

Frequently there are multiple emboli, perhaps sequentially or as a shower of smaller emboli from a single large mass; in general, *the patient who has had one PE is at high risk of having more*. Rarely, an embolus can pass through an interatrial or interventricular defect and gain access to the systemic circulation (*paradoxical embolism*). (Ref: Robbins & Cotran-9<sup>th</sup>, P-127)

**Clinical Effects:**

- Most pulmonary emboli (60% to 80%) are clinically silent because they are small. With time they become organized and are incorporated into the vascular wall; in some cases organization of the thromboembolus leaves behind a delicate, bridging fibrous web.
- Sudden death, right heart failure (*cor pulmonale*), or cardiovascular collapse occurs when emboli obstruct 60% or more of the pulmonary circulation.
- Embolic obstruction of medium-sized arteries with subsequent vascular rupture can result in pulmonary hemorrhage but usually does not cause pulmonary infarction. This is because the lung has a dual blood supply, and the intact bronchial circulation continues to perfuse the affected area. Understandably, if the bronchial arterial flow is compromised (e.g., by left-sided cardiac failure), infarction may occur.
- Embolic obstruction of small end-arteriolar pulmonary branches usually does result in hemorrhage or infarction.
- Multiple emboli over time may cause pulmonary hypertension and right ventricular failure.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-127)

**■ Commonest sources of thrombo-emboli:****A. Pulmonary thromboemboli:**

- Large deep veins at or above the knee (e.g. popliteal, femoral & iliac veins)
- Calf veins.
- Superficial varicose vein
- Pelvic veins

**B. Systemic thromboemboli:**

- From heart thrombi: left ventricle (MI), left atrium (rheumatic heart disease), valvular prostheses.
- Artery: atherosclerotic plaques, aortic aneurysm.

(Ref: Robbins & Cotran-9<sup>th</sup>)

**FAT EMBOLISM****Q. Fat embolism syndrome is characterized by (BSMMU – Non-Residency - MD/MS, Basic science – 13Ju)**

- |  |   |
|--|---|
| a) pulmonary insufficiency             | T |
| b) neurological symptoms               | T |
| c) anaemia                             | T |
| d) painful conditions called the bends | F |
| e) decompression sickness              | F |

**HELP LINK:****Fat embolism:**

- Microscopic fat globules – sometimes with associated hematopoietic marrow elements—can be found in the circulation and impacted in the pulmonary vasculature after fractures of long bones (which have fatty marrow) or, rarely, in the setting of soft tissue trauma and burns.

- Presumably these injuries rupture vascular sinusoids in the marrow or small venules, allowing marrow or adipose tissue to herniate into the vascular space and travel to the lung.
- Fat and marrow emboli are very common incidental findings after vigorous cardiopulmonary resuscitation and are probably of no clinical consequence. Indeed, fat embolism occurs in some 90% of individuals with severe skeletal injuries, but less than 10% of such patients have any clinical findings.

**Causes:**

1. Fracture of shafts of long bones which have fatty marrow.
2. Trauma of adipose tissue.
3. Burn of adipose tissue.

**Pathogenesis:**

1. **Mechanical obstruction:** Fat microemboli and associated red cell and platelet aggregates can occlude the pulmonary and cerebral microvasculature.
2. **Biochemical injury:** Release of free fatty acids from the fat globules exacerbates the situation by causing local toxic injury to endothelium, and platelet activation and granulocyte recruitment (with free radical, protease, and eicosanoid release) complete the vascular assault.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-128)

**Clinical features:** Fat embolism syndrome is the term applied to the minority of patients who become symptomatic.

**Fat embolism syndrome:**

- It is characterized by pulmonary insufficiency, neurologic symptoms, anemia, and thrombocytopenia, and is fatal in about 5% to 15% of cases.
- Typically, 1 to 3 days after injury there is a sudden onset of tachypnea, dyspnea, and tachycardia; irritability and restlessness can progress to delirium or coma.
- Thrombocytopenia is attributed to platelet adhesion to fat globules and subsequent aggregation or splenic sequestration; anemia can result from similar red cell aggregation and/or hemolysis.
- A diffuse petechial rash (seen in 20% to 50% of cases) is related to rapid onset of thrombocytopenia and can be a useful diagnostic feature.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-128)**Morphology:**

1. **Lung:** Marked oedema and hyaline membranes in the alveoli.
2. **Kidney:** Globules in glomeruli.
3. **Brain:** Microemboli of fat, cerebral oedema, perivascular microhaemorrhages, and microinfarcts.
4. **Skin, conjunctivae and serosal membranes - Petechiae.**

(Ref: Robbins & Cotran-9<sup>th</sup>, P-128)

**Q. Fat embolism syndrome is characterized by:** (BSMMU - MD/MS - January, 2009)

- |                                       |   |
|---------------------------------------|---|
| a) decompression sickness             | F |
| b) pulmonary insufficiency            | T |
| c) neurologic symptoms                | T |
| d) anemia                             | T |
| e) painful condition called the bends | F |

**Q. Fat embolism - (DMC - M. phil, Diploma - 03Ju)**

- |  |              |
|--|--------------|
| a) Occurs as a result of fractures of bones            | T            |
| b) Diagnosed by the detection of fat globules in urine | T            |
| c) Occurs about 10 days after injury                   | F (1-3 days) |
| d) Is fatal due to pulmonary insufficiency             | T            |
| e) Causes disseminated intravascular coagulation       | T            |

**Q. Fat embolism- (BSMMU-MS-02Ja)**

- |   |                  |
|---|------------------|
| a) Occurs two hours after injury                        | F                |
| b) Occurs two days after injury                         | T (1 - 3 days)   |
| c) Causes mainly cerebral symptoms.                     | F                |
| d) Causes mainly chest symptoms.                        | F                |
| e) The most important physical sign is a petechial rash | T (20-50% cases) |

**Help link:** Both cerebral and chest symptoms are developed mostly due to thrombocytopenia.

**Q. Fat embolism:** (MD/MS (DMC)-02Ja)

- A. Occurs two hours after injury.
- B. Occurs two days after injury.
- C. Causes mainly chest symptoms.
- D. Causes mainly cerebral symptoms.
- E. The most important physical sign is petechial rash.

**Ans.**

- a) F (multiple fracture, soft tissue trauma, burn are the common cause)
- b) T c) F d) F e) T

**Q. Fat embolism common in:** (MD/MS(DMC)-01Ja)

A. Fracture	T
B. Blood transfusion	F
C. I-V infusion	F
D. Deep vein thrombosis	F
E. Thrombophlebitis	F

## Air Embolism

- ✓ Gas bubbles to form coalesce and obstruct the vascular flow causes ischaemic injury.
- ✓ 100 cc air is necessary to produce clinical syn. (normally neurosurgery and bypass surgery less than 100 cc air trapped)
- ✓ **Decompression sickness:**
  - I. decreased atmospheric pressure
  - II. High risk: scuba and deep sea divers, underwater construction worker, aircraft in rapid ascent
  - III. Mechanisms: air breath at high pressure, N2 dissolves in blood and tissues, when depressures rapidly, N2 comes out to form bubble
- ✓ **Acute decompression sickness:**
  - I. Bends: rapid formation of gas bubble in muscle and joints, painful
  - II. Chokes: in the lungs, gas bubble produces oedema, Hge, focal atelectasis or emphysema, leads to respiratory distress.
- ✓ **Chronic decompression sickness:**
  - I. Caisson disease-
  - II. high risk: in bridge construction worker,
  - III. common sites: femoral head, tibia, humerus
  - IV. pathology: persistence of gas bubble in skeletal system leads to ischaemic necrosis

## Amniotic fluid embolism

**Q. Amniotic fluid embolism causes** (BSMMU – Non-Residency – MS, Basic Science – July' 17)

- a) severe dyspnoea
- b) hypertension
- c) peripheral cyanosis
- d) pulmonary hypertension
- e) bronchodilatation

Ans. a) T b) F c)T d) F e)F

**Help link:**

- ✓ 5<sup>th</sup> most common cause of maternal mortality
- ✓ When seen: complication of labour, immediate post partum period
- ✓ **Clinical features:** sudden severe dyspnoea, cyanosis, shock, headache, seizure, coma.
- ✓ Complication: pulmonary oedema, DIC

- ✓ Mechanisms: infusions of amniotic fluid into the maternal circulation via tearing of placental membrane or rupture of uterine veins.
- ✓ On autopsy:
  - ❖ presence of squamous cells from fetal skin, lanugo hair, fat from vernix caseosa, mucin from fetal GIT or respiratory system.
  - ❖ Others: marked pul. Oedema, diffuse alveolar damage, fibrin thrombi due to DIC.

(Ref: Robbins-9<sup>th</sup>, P-129)

## INFARCTION

### INFARCTION

■ **Definition:** An infarct is an area of ischemic necrosis caused by occlusion of either the arterial supply or the venous drainage.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-129)

#### Examples:

- myocardial infarction
- cerebral infarction.
- Pulmonary infarction
- bowel infarction
- ischemic necrosis of the extremities (*gangrene*)

(Ref: Robbins & Cotran-9<sup>th</sup>, P-129)

#### Causes of infarction:

- ❖ Arterial thrombosis or embolism(majority cause),
- ❖ Less common:
  - ❖ local vasospasm,
  - ❖ Hge into an ulcerated atheromatous plaque,
  - ❖ by tumour compression,
- ❖ Uncommon cause:
  - ❖ testicular torsion or bowel volvulus,
  - ❖ traumatic vascular rupture,
  - ❖ anterior compartment syndrome

#### ■ Classification:

##### A. *On the basis of color:*

1. Red (hemorrhagic) infarct
2. White or pale (anaemic) infarct.

##### B. *On the basis of bacterial contamination:*

1. Septic: bacterial infection present.
2. Bland: bacterial infection absent.

##### C. *On the basis of duration:*

1. Recent infarct.
2. Old infarct.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-129)

#### Morphology of an infarct:

##### A. Macroscopic:

- **Shape:** Infarcts tend to be wedge-shaped, with the occluded vessel at the apex and the periphery of the organ forming the base; when the base is a serosal surface there can be an overlying fibrinous exudate.

##### • Color:

Time	Red infarct	White infarct
Few hours	Slightly darker	Slightly darker
24 hours	More intense	More intense
Several days	Yellow white	Red

- **Margin:** Hyperemic (due to inflammation)

- **Consistency:** firmer than the surrounding tissue due to coagulative necrosis.

**B. Microscopic:****■ All infarcts (except brain):**

- Coagulative necrosis.
- Inflammatory reaction at periphery
- Then fibroblastic response at the periphery.
- Then the focus becomes fibrotic.

**■ Infarction of brain:** Liquefactive necrosis**■ Septic infarction:** Liquefactive necrosis.(Ref: Robbins & Cotrans-9<sup>th</sup>, P-129-130)**Red (hemorrhagic) infarct commonly occurs in the following situations-**

- (1) with venous occlusions (e.g., ovary),
- (2) in loose tissues (e.g., lung) where blood can collect in the infarcted zone,
- (3) in tissues with dual circulations (e.g., lung and small intestine) that allow blood flow from an unobstructed parallel supply into a necrotic zone,
- (4) in tissues previously congested by sluggish venous outflow, and
- (5) when flow is re-established to a site of previous arterial occlusion and necrosis (e.g., following angioplasty of an arterial obstruction).

**White infarcts** occur with arterial occlusions in solid organs with end-arterial circulation (e.g., heart, spleen, and kidney), and where tissue density limits the seepage of blood from adjoining capillary beds into the necrotic area.(Ref: Robbins & Cotrans-9<sup>th</sup>, P-129-130)

Traits	Red infarct	White infarct
1. Cause	Venous occlusion	Arterial occlusion
2. Organs involved	Lungs, small intestine, brain, ovary	heart, spleen, and kidney
3. Colour (After 24 to 48 hours)	red	pale

(Ref: Robins & Cotrans-9<sup>th</sup>, P-129, 130; Prof. Khaleque-45,46)**Question Bank****Q. Red infarct is seen in (BSMMU-Residency – MD, MS, Basic Science – March' 18)**

- a) heart
- b) lung
- c) brain
- d) ovary
- e) small intestine

Ans. a) F b) T c) T d) T e) T

**Q. An infarct (BSMMU-Residency - MD/MS, Basic science – March' 14)**

- a) is a localized area of ischaemic necrosis
- b) develops rapidly in tissues with dual blood supply
- c) in solid organs are red in appearance
- d) is usually wedge shaped
- e) of myocardium leads to scar formation

Ans. a) T b) F (slowly develops) c) F d) T

e) T (inflammatory reactions are present in surrounding the tissue)

**Q. Red infarct occurs in: (BSMMU – Residency – MD/MS – March'13)**

- a) Lung
- b) Heart
- c) Spleen
- d) Intestine
- e) Tissue previously congested

Ans : a) T b) F c) F d) T e) T

**Q. In cerebral infarction:** (BSMMU – M. Phil, Diploma (Non-Residency) – I2Ju, DMC & others – MD/MS – I2Ju)

- a) the infarcted area is wedge shaped
- b) coagulative necrosis is seen in brain tissue
- c) the affected area can be either haemorrhagic or pale
- d) thrombosis of internal carotid artery is a common cause
- e) necrosed tissue is replaced by new neurons

**Ans.** a) T (always liquifactive necrosis, also in any abscess cavity)

b) F c) T d) T e) F

**Q. Necrosis in a solid organ due to ischemia-** (BSMMU - MD - January - 11)

- |                                      |                        |
|--------------------------------------|------------------------|
| a) is called infarction              | T                      |
| b) is dusky red in color             | F (pale)               |
| c) is coagulative in nature          | T (Ischaemic necrosis) |
| d) is reversed by reperfusion        | F                      |
| e) does not produce any inflammation | F                      |

**Q. Infarction usually occurs in the following setting:** (BSMMU - M. Phil, Diploma, July'08)

- |  |   |
|--|---|
| a) tissue with double blood supply                               | F |
| b) tissue suffers from sudden occlusion of arterial blood supply | T |
| c) patient with severe anemia                                    | T |
| d) tissue with venous obstruction                                | T |
| e) tissue with gradual obstruction of its arterial blood supply  | F |

**Q. Haemorrhagic infarct is found in** (M. phil, Diploma – 03Ju)

- |                         |   |
|-------------------------|---|
| a) Twisted ovarian cyst | T |
| b) Lung                 | T |
| c) Small intestine      | T |
| d) Heart                | F |
| e) Kidney               | F |

**Q. Major factors influencing development of infarct are-** (BSMMU-MD/MS - 02Ja)

- |                                  |   |
|----------------------------------|---|
| a) Nature of vascular supply     | T |
| b) Source of emboli              | F |
| c) Rate of development occlusion | T |
| d) Vulnerability of the tissue   | T |
| e) Amount of blood loss          | F |

**Help link:**

**Factors influencing development of infarct:**

**1. Anatomy of the vascular supply.** The availability of an alternative blood supply is the most important determinant of whether vessel occlusion will cause damage.

- Dual circulation (e.g. in lungs, liver, hand and forearm) are all relatively resistant to infarction.
- In contrast, renal and splenic circulations are end-arterial, and vascular obstruction generally causes tissue death.

**2. Rate of occlusion.** Slowly developing occlusions are less likely to cause infarction, because they provide time to develop alternate perfusion pathways. For example, Collateral coronary circulation.

**3. Tissue vulnerability to hypoxia:**

- Neurons undergo irreversible damage when deprived of their blood supply for only 3 to 4 minutes. Myocardial cells, though hardier than neurons, are also quite sensitive and die after only 20 to 30 minutes of ischemia.
- In contrast, fibroblasts within myocardium remain viable even after many hours of ischemia.

**4. Hypoxemia:** Abnormally low blood O<sub>2</sub> content (regardless of cause) increases both the likelihood and extent of infarction.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-130-131)

**Q. Pale infarcts are found in - (BSMMU-MS-01Ja)**

- |                    |   |
|--------------------|---|
| a) Heart           | T |
| b) Lung            | F |
| c) Spleen          | T |
| d) Kidney          | T |
| e) Small intestine | F |

**Help link:** Pale infarcts are found in solid organs.

## SHOCK

**Shock** is a state in which diminished cardiac output or reduced effective circulating blood volume impairs tissue perfusion and leads to cellular hypoxia.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-131)

**Classification with causes:**

Types of shock	Clinical Example	Principal Mechanisms
<b>Major three types</b>		
<b>Cardiogenic</b>	Myocardial infarction Ventricular rupture Arrhythmia Cardiac tamponade Pulmonary embolism	Failure of myocardial pump resulting from intrinsic myocardial damage, extrinsic pressure, or obstruction to outflow
<b>Hypovolemic</b>	Fluid loss (e.g., hemorrhage, vomiting, diarrhea, burns, or trauma)	Inadequate blood or plasma volume
<b>Shock associated with systemic inflammation (Septic shock)</b>	Overwhelming microbial infections (bacterial and fungal) Superantigens (e.g., toxic shock syndrome) Trauma, burns, pancreatitis	Activation of cytokine cascades; peripheral vasodilation and pooling of blood; endothelial activation/injury; leukocyte-induced damage, disseminated intravascular coagulation.
<b>Less commonly</b>		
<b>Neurogenic shock</b>	anesthetic accident spinal cord injury	
<b>Anaphylactic shock</b>	IgE-mediated hypersensitivity reaction	

(Ref: Robbins & Cotran-9<sup>th</sup>, P-131)

**Types of shock, with examples of conditions or diseases that can cause each type**

**Hypovolemic shock (decreased blood volume)**

- Hemorrhage      • Trauma
- Surgery           • Burns
- Fluid loss due to vomiting or diarrhea

**Distributive shock (marked vasodilation; also called vasogenic or low-resistance shock)**

- Fainting (neurogenic shock)
- Anaphylaxis
- Sepsis (also causes hypovolemia due to increased capillary permeability with loss of fluid into tissues)

**Cardiogenic shock (inadequate output by a diseased heart)**

- Myocardial infarction
- Congestive heart failure
- Arrhythmias

**Obstructive shock (obstruction of blood flow)**

- Tension pneumothorax
- Pulmonary embolism
- Cardiac tumor
- Cardiac tamponade

(Ref: Ganong-24<sup>th</sup>)

**■ Morphologic changes occur in different organs due to shock:**

- Changes can manifest in any tissue although they are particularly evident in brain, heart, lungs, kidneys, adrenals, and gastrointestinal tract.

1. **Brain:** ischemic encephalopathy

2. **Heart:**

- Focal or widespread coagulation necrosis
- Subendocardial haemorrhage and/or
- Contraction band necrosis

3. **Lungs:**

- Seldom affected in pure hypovolemic shock.
- Acute respiratory distress syndrome
- In septic shock - **diffuse alveolar damage** (shock lung)

4. **Kidneys:**

- Acute tubular necrosis.
- Oliguria/ anuria
- Electrolytes imbalance

5. **Adrenal gland:** cortical cell lipid depletion.

6. **GIT:** Patchy mucosal hemorrhage and necrosis (haemorrhagic enteropathy)

7. **Liver:**

- Fatty change
- In severe case – central hemorrhagic necrosis

8 **Skin:** In septic shock - petechial hemorrhages on serosal surface and the skin.

**(Ref: Robbins & Cotran-9<sup>th</sup>, P-134)**

**Compensatory reactions activated by haemorrhage:**

- Vasoconstriction
- Tachycardia
- Venoconstriction
- Tachypnea → increased thoracic pumping
- Restlessness → increased skeletal muscle pumping (in some cases)
- Increased movement of interstitial fluid into capillaries
- Increased secretion of vasopressin
- Increased secretion of Glucocorticoids
- Increased secretion of rennin and aldosterone
- Increased secretion of erythropoietin
- Increased plasma protein synthesis.

**Question Bank**

**Q. In hypovolemic shock, patients present with (BSMMU –Residency - MD/MS, Basic science, Paediatrics,**

*Dentistry – March '19)*

- a) hypotension
- b) cool and clammy skin
- c) hyperthermia
- d) tachypnea
- e) bradycardia

**Ans. a) T b) T c) F(cold and clammy skin) d) T e) F(tachycardia)**

**Q. Followings are early features of shock (BSMMU – Residency - Basic science – March' 19)**

- a) tachycardia
- b) cool periphery
- c) prolonged capillary refilling time
- d) low blood pressure
- e) end organ failure

Ans. a) T b) T c) T d) T e) F (late features)

**Q. Shock is characterized by (BSMMU – Non-Residency – MD, MS, Basic science, Dentistry – July' 18)**

- a) hypoperfusion
- b) cellular hypoxia
- c) hypertension
- d) loss of vascular tone
- e) increased cardiac output

Ans. a) T b) T c) F

d) T (**Distributive (or vasogenic) shock** is caused by a sudden severe decrease in peripheral vascular resistance that causes extensive pooling of blood)

e) F

**Q. Causes of hypovolemic shock (BSMMU – M. Phil, Diploma (Non-Residency) – March-2012)**

- |                            |                       |
|----------------------------|-----------------------|
| a) burn injury             | T                     |
| b) intestinal fistula      | T                     |
| c) spinal cord transaction | F (Anaesthetic shock) |
| d) myocardial infarction   | F (Cardiogenic shock) |
| e) endotoxaemia            | F (Septic shock)      |

**Q. In a state of shock there is – (MD/MS (DMC)- 08Ja)**

- |   |                             |
|---|-----------------------------|
| a) fall in blood fatty acid level       | T                           |
| b) fall in blood amino acid level       | F (Increase plasma protein) |
| c) metabolic acidosis                   | T                           |
| d) entry of lactic acid into kreb cycle | T                           |
| e) increase catecholamine level         | T                           |

**Help link:**

**Patho-physiology of shock:**

**1. Cellular:** Perfusion to the tissues is reduced → cells are deprived of oxygen → switch from aerobic to anaerobic metabolism → accumulation of lactic acid in the blood → systemic metabolic acidosis glucose within cells is exhausted, anaerobic respiration ceases → failure of the sodium/potassium pumps in the cell membrane and intracellular organdies → intracellular lysosomes release autodigestive enzymes and cell lysis ensues.

**2. Microvascular:** As tissue ischaemia progresses, hypoxia and acidosis activate complement and prime neutrophils → generation of oxygen free radicals and cytokine release → these mechanisms lead to injury of the capillary endothelial cells → these in turn further activate the immune and coagulation systems → damaged endothelium loses its integrity and becomes ‘leaky’ → spaces between endothelial cells allow fluid to leak out and tissue oedema ensues, exacerbating cellular hypoxia.

**3. Systemic:**

- a) **Cardiovascular:** As preload and afterload decrease there is a compensatory baroreceptor response resulting in increased sympathetic activity → release of catecholamines into the circulation → tachycardia and systemic vasoconstriction.
- b) **Respiratory:** The metabolic acidosis and increased sympathetic response → increased respiratory rate and minute ventilation → increase the excretion of carbon dioxide.

c) **Renal:** Decreased perfusion pressure in the kidney → reduced filtration at the glomerulus and a decreased urine output → rennin-angiotensin axis is stimulated → further vasoconstriction and increased sodium and water reabsorption by the kidney.

d) **Endocrine:**

- Vasopressin (ADH) is released from the hypothalamus in response to decreased preload → vasoconstriction and reabsorption of water in the renal collecting system.
- Cortisol is also released from the adrenal cortex → sodium and water reabsorption increases.

(Ref: Bailey & Love's-27<sup>th</sup>, P-13)

## Stages of shock

**Q. In progressive stage of shock (BSMMU – Residency – MD, MS, Basic science, Dentistry – March' 16; Non-Residency – MD/MS, Basic science – July' 14; M. Phil, Diploma (Non-Residency)–March-2012, DMC & others – MD/MS – March-2012, Non-Residency – I1Ju., Residency – I1Ja)**

- a) there is metabolic acidosis
- b) reflex compensatory mechanisms are activated
- c) there is wide spread tissue hypoxia
- d) survival is possible
- e) there is complete renal shut down

Ans. a) T b) F c) T d) T e) F

**HELP LINK:**

**Stages of shock:**

- An initial **nonprogressive phase** during which reflex compensatory mechanisms are activated and perfusion of vital organs is maintained
- A **progressive stage** characterized by tissue hypoperfusion and onset of worsening circulatory and metabolic imbalances, including acidosis
- An **irreversible stage** that sets in after the body has incurred cellular and tissue injury so severe that even if the hemodynamic defects are corrected, survival is not possible.

(Ref: Robbins & Cotran's-9<sup>th</sup>, P-133)

If the underlying causes are not corrected, shock passes imperceptibly to the progressive phase, during which there is widespread tissue hypoxia. In the setting of persistent oxygen deficit, intracellular aerobic respiration is replaced by anaerobic glycolysis with excessive production of lactic acid. The resultant metabolic lactic acidosis lowers the tissue pH and blunts the vasomotor response; arterioles dilate, and blood begins to pool in the microcirculation.

Peripheral pooling not only worsens the cardiac output, but also puts endothelial cells at risk for developing anoxic injury with subsequent DIC. With widespread tissue hypoxia, vital organs are affected and begin to fail; clinically the patient may become confused, and the urine output declines.

**Early non-progressive shock:**

- Neurohumoral mechanism is activated
- Perfusion of vital organs maintained
- Maintain CO and BP
- Baroreceptor reflexes activate
- Catecholamine release
- Activation of renin angiotensin mechanism
- ADH release
- Sympathetic stimulation
- Tachycardia, peripheral vasoconstriction
- Renal conservation of fluid

- Cutaneous vasoconstriction leads to coolness and pallor of skin (but in septic shock- initially cutaneous vasodilatation, leads to warm and flushed skin)
- Coronary and cerebral vessels are less sensitive to sympathetic response.

**Progressive shock:**

- Widespread tissue hypoxia
- Anaerobic glycolysis
- Lactic acidosis(decreased PH)
- Blunt vasomotor response
- Arterioles dilate
- Peripheral pooling of blood
- Anoxic injury to endothelium leads to DIC

**Irreversible stage of shock:**

- Survival is not possible
- Lysosomal enzymes leakage
- Intestinal flora comes from ischaemic bowel to circulation leads to sepsis
- Anuria
- Acute tubular necrosis(ATN) and RF
- Death
- Neuronal and myocardial ischaemic loss can not revert.

**Q. In progressive phase of shock - (BSMMU – MD/MS - January, 2009)**

- |   |   |
|---|---|
| a) there is widespread tissue hypoxia           | T |
| b) survival is not possible                     | F |
| c) there is complete renal shutdown             | F |
| d) there is metabolic acidosis                  | T |
| e) reflex compensatory mechanisms are activated | F |

## Hypovolaemic shock

**Q. Compensated hypovolaemic shock is characterized by (BSMMU – Residency – MS – March' 16)**

- |                            |   |
|----------------------------|---|
| a) anxiety                 | T |
| b) hypotension             | F |
| c) low urine output        | F |
| d) normal respiratory rate | T |
| a) tachycardia             | T |

**Q. General features of hypovolemic shock include - (BSMMU - M. Phil, Diploma, July-07)**

- |                                   |   |
|-----------------------------------|---|
| a) hypotension                    | T |
| b) bradycardia                    | F |
| c) rapid shallow respiration      | T |
| d) raised jugular venous pressure | F |
| e) oliguria                       | T |

**Help link:**

**General features of hypovolemic shock:**

- Pulse increased
- Decreased BP
- Low urinary output
- Cold clammy skin
- Rapid shallow breathing (tachypnea)
- 90 % hypovolumic shock pts can survive with treatment.

## SEPTIC SHOCK

**Q. Septic shock (BSMMU – Residency – Dentistry – March '18)**

- a) is synonymous to endotoxic shock
- b) is most frequently triggered by gram-negative bacteria
- c) can lead to ARDS
- d) leads to adrenal insufficiency
- e) can lead to multi-organ failure

Ans. a) T b) T c) T d) T e) T

### HELP LINK:

*Septic shock* results from vasodilation and peripheral pooling of blood as part of a systemic immune reaction to bacterial or fungal infection.

■ **Etiology:** Currently, septic shock is most frequently triggered by gram-positive bacterial infections, followed by gram-negative bacteria and fungi. Hence, the older synonym of “endotoxic shock” is not appropriate.

(Ref: Robbins & Cotran's-9<sup>th</sup>, P-131)

#### **Causing agents:**

1. Endotoxin producing gram negative bacilli (E.coli, proteus, pseudomonas)
2. Some gram positive cocci (Streptococci, pneumococci)
3. Toxic shock syndrome toxin-I of Staph. Aureus
4. Some fungi.

#### ■ **Pathogenesis of septic shock:**

Endotoxins (bacterial wall LPSs) are released when the cell wall are degraded from the organisms after an infection



Free lipopolysaccharide (LPS) attaches to a circulating LPS-binding protein



The complex then binds to a cell-surface receptor (called CD 14) on leukocytes (specially monocytes & macrophages), endothelial cells and other cell types



Initiation of synthesis, release or activation of cascade of cytokine mediators (TNF, IL-1, IL-6, and chemokines), complement, nitric oxide, prostaglandins etc.



Systemic vasodilation (hypotension)

Diminished myocardial contractility

Widespread endothelial injury and activation causing acute respiratory distress syndrome (ARDS)

Activation of the coagulation system, culminating in DIC



Hypoperfusion



Multiple organ system failure affecting the liver, kidneys, and central nervous system, among others

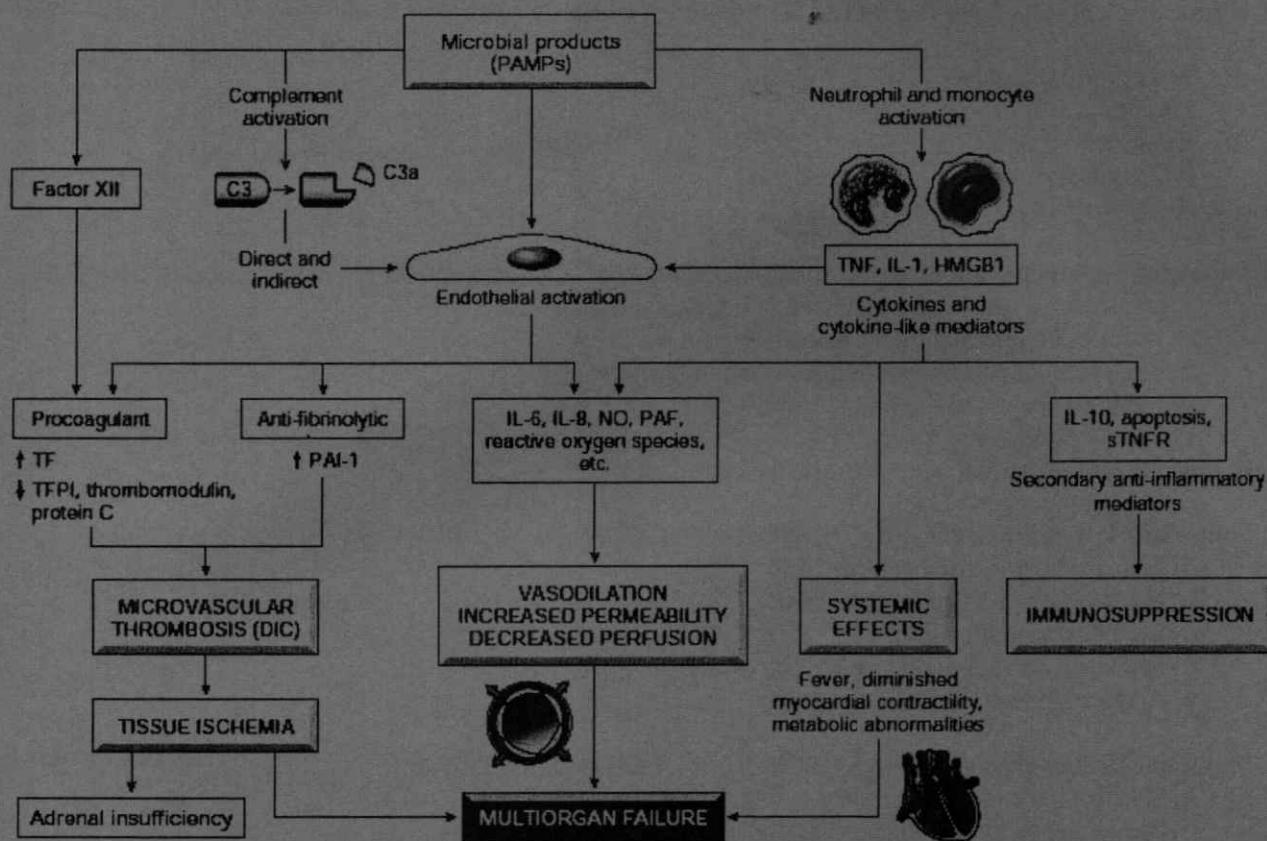


Septic shock



Death (near 20%)

(Ref: Robbins-9<sup>th</sup>, P-131, 132; 8<sup>th</sup>-130-132 + 7<sup>th</sup>/139,140)



**Figure: Major pathogenic pathways in septic shock.** Microbial products (PAMPs, or pathogen-associated molecular patterns) activate endothelial cells and cellular and humoral elements of the innate immune system, initiating a cascade of events that lead to end-stage multiorgan failure. Additional details are given in the text. DIC, Disseminated vascular coagulation; HMGB1, high mobility group box 1 protein; NO, nitric oxide; PAF, platelet activating factor; PAI-1, plasminogen activator inhibitor 1; TF, tissue factor; TFPI, tissue factor pathway inhibitor.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-132)

#### ■ End results of septic shock:

1. Recovery
2. Death due to
  - Refractory hypotension
  - Multiple organ failure (kidney, brain, heart, adrenal gland etc)

**Mediators of septic shock:** The mediators that have been implicated in causing septic shock include the following:

1. Cytokines (IL-1, TNF- $\alpha$ , IL-6, IL-8)
2. Platelet activating factor
3. Nitric oxide
4. Complement (C5a and C3a)
5. Prostaglandins
6. Leukotrienes
7. The kinin systems
8. Oxygen metabolites
9. Catecholamines
10. Endorphines
11. Myocardial depressant factors

(Ref: Robbins & Cotran-9<sup>th</sup>, P-131)

**Q. Septic shock results from the spread of: (BSMMU – Residency – MD/MS – March'13)**

- a) An abscess
- b) Myocardial infarction
- c) Peritonitis
- d) Keratitis
- e) Pneumonia

Ans : a) T b) F c) T d) F e) T

**Q. Following statements about septic shock are true (BSMMU – MD/MS (Residency) – January, 2011)**

- |   |   |
|---|---|
| a) results from spread of a localized infection into bloodstream. | T |
| b) it causes endothelial injury activation.                       | T |
| c) it inhibits coagulation system resulting in bleeding.          | F |
| d) it reduces myocardial contractility                            | T |
| e) it induces neuronal trauma                                     | T |

**Help link:** Increased procoagulant activity, in septic shock.

**Q. Septic shock is characterized by - (BSMMU-MD/MS-07Ja)**

- |  |   |
|--|---|
| a) Increased myocardial contractility  | F |
| b) Inactivation of coagulation system  | F |
| c) Systemic vasodilatation             | T |
| d) Wide spread endothelial injury      | T |
| e) Acute respiratory distress syndrome | T |

**Q. Septic shock is characterized by - (BSMMU - M. Phil, Diploma, July-06)**

- |  |   |
|--|---|
| a) Widespread endothelial injury       | T |
| b) Systemic vasodilatation             | T |
| c) Increased myocardial contractility  | F |
| d) Inactivation of coagulation system  | F |
| e) Acute respiratory distress syndrome | T |

## IMPORTANT MCQ OF HAEMODYNAMIC DISORDERS

[Ref: Smiddy]

**Q. Oedema occurs in:**

- a) Cushing's syndrome
- b) Conn's syndrome
- c) Zollinger—Ellison syndrome
- d) Klinefelter's syndrome
- e) pregnancy

Ans.

- a) **True** Cushing's syndrome is caused by the excessive secretion of both mineralo- and gluco-corticoids by the adrenal cortex, due to hyperplasia, an adenoma or a malignant tumour. Sodium retention follows, with the result that oedema develops. Additional factors are the associated hypertension and a chemical change of the interstitial tissues allowing more fluid retention.
- b) **False** Conn's syndrome or primary hyperaldosteronism is associated with a cortical adenoma or bilateral zona glomerulosa hyperplasia. It normally presents with either hypertension or the symptoms of hypokalaemia (muscle weakness or paralysis). Sodium and water retention occurs which causes the hypertension, but oedema does not develop because of increasing sodium excretion by the kidneys.
- c) **False** The Zollinger—Ellison syndrome is caused by hyperplasia, benign adenoma or a malignant tumour of the D cells of the pancreas. This results in the secretion of large amounts of gastrin which in turn stimulates the parietal cells causing them to secrete acid at their maximal capacity. So great is the output, that the pH of the upper jejunum may be less than 2 at which point pancreatic lipase is

inactivated and bile salts may be precipitated causing steatorrhoea. The pathological result of the excessive acid secretion is usually multiple ulceration which may develop in abnormal situations.

- d) False** This syndrome is not associated with oedema. It is one of the commonest chromosomal disorders resulting from the presence of a Y chromosome together with a second X, the Y chromosome ensuring the formation of the testes and masculine development but the second X preventing the development of the testes.
- e) True** Pregnancy is associated with fluid retention which thus gives rise to oedema particularly in the dependent parts. In late pregnancy hypertension and pre-eclampsia may lead to worsening of the condition.

**Q. Angioneurotic oedema is associated with:**

- depression
- complement deficiency
- immunoglobulin E
- menstruation
- NSAID poisoning

**Ans.**

- a) False** Although the term 'angioneurotic' may suggest an underlying psychiatric disorder, this is not so. The term is used to describe an oedema, mainly of an urticarial type which is frequently seen on the face and neck. The more recent term to describe the condition is angio-oedema.
- b) False** Complement is normal in angio-oedema but in the hereditary form which is an autosomal dominant condition there is a deficiency of C1 inhibitor. This permits complement activation to go unchecked and the mast cells to degranulate, liberating vasoactive peptides. In this condition sporadic attacks particularly affecting the face and gut occur.
- c) True** Urticarial angio-oedema is relatively common in atopic children, the term used to describe 10-15% of the population who suffer from allergic disorders including angio-oedema, asthma, eczema and food allergies. The development of the angio-oedema follows the ingestion of food allergens and is mediated by IgE. The IgE causes the degradation of mast cells with the release of vasoactive amines.
- d) False** The salt and water retention associated with the premenstrual period are normally not associated with increased capillary permeability and oedema.
- e) False** The common clinical features of poisoning with non-steroidal anti-inflammatory agents are nausea and vomiting, gastrointestinal haemorrhage, headache, tinnitus, disorientation, confusion and haematuria associated with renal failure. Hepatic dysfunction can also be caused together with a metabolic acidosis.

**Q. Pulmonary oedema may occur in patients suffering from:**

- major trauma
- plague
- right-sided heart failure
- hypoproteinaemia
- nematode infections

**Ans.**

- a) True** Patients suffering from multiple injuries may develop the condition of shock lung, now more commonly known as ARDS, Adult Respiratory Distress Syndrome. Initially there are few if any pulmonary symptoms but these usually develop within 48 hours. Even when the patient is complaining of dyspnoea and tachycardia, the appearance of the chest x-ray may be normal. Later as pulmonary oedema develops, patchy infiltrates appear. These develop due to an increase in capillary permeability due to a variety of factors including cytokines, oxygen radicals, complement and arachidonate metabolites.
- b) True** Pulmonary oedema is a pathological facet of pneumonic plague caused by *Yersinia pestis*, a Gram-negative facultative intracellular bacterium transmitted by flea bites. The major pulmonary pathology is the development of a severe confluent haemorrhagic and necrotising bronchopneumonia.

- c) False** Pulmonary oedema occurs in left-sided heart failure and is most commonly seen in patients suffering from a failing heart due to hypertension, aortic valvular disease or following a myocardial infarct. The clinical manifestations in the early stages occur at night, causing attacks of nocturnal dyspnoea (cardiac asthma). Pathologically fluid initially accumulates in the basal regions of the lower lobes because hydrostatic pressure is greatest in these areas. Histologically the alveolar capillaries are engorged and haemosiderin-laden macrophages (heart failure cells) may be seen.
- d) False** Hypoproteinaemia does not specifically cause pulmonary oedema except as a terminal event when cardiac failure occurs. However, hypoproteinaemia is associated with peripheral dependent oedema.
- e) False** Nematode larvae of ankylostomes and ascaris may migrate through the lungs and cause pulmonary eosinophilia. This may be associated with pneumonic consolidation but there is no evidence that they cause pulmonary oedema.

**Q. Amyloid is deposited most frequently in:**

- a) liver
- b) brain
- c) spleen
- d) lungs
- e) kidneys

Ans.

- a) True** Amyloidosis of the liver is not necessarily associated with hepatomegaly. The material is first seen in the Space of Disse and then progressively encroaches into the adjacent hepatic parenchymal cells and sinusoids causing progressive deformity and pressure atrophy. The cut surface of the liver has a waxy refractile appearance. Despite advanced disease, liver function is not usually severely impaired.
- b) True** Although the CNS is not usually affected by amyloidosis, a condition known as amyloid angiopathy is almost invariably found in Alzheimer's disease, immunohistological staining for amyloid beta-peptide showing the deposition of amyloid in the walls of the smaller cortical vessels.
- c) True** Amyloid deposits in the spleen take two forms. In one the Malpighian bodies are changed into translucent globules by amyloid deposition in their reticulum, hence the term sago spleen, in which splenomegaly is not marked. In the other form the change affects the reticulum of the red pulp, the walls of the venous sinuses and many of the small arteries. In this latter type the spleen may be palpable and weigh up to 1 kg; this is a rarer condition than the sago spleen and is only common in tertiary syphilis.
- d) False** The lungs are an infrequent site of amyloid deposition although deposits may occur in primary amyloidosis, i.e. amyloidosis occurring in the absence of any predisposing cause.
- e) True** Renal amyloidosis is particularly important because once established, renal failure is almost inevitable and indeed renal amyloidosis is the most frequently recorded cause of death. The kidneys may be of normal size, enlarged or lastly shrunken owing to the deposition of amyloid within the arterial and arteriolar walls. The initial deposits of amyloid appear in the glomeruli causing distortion but the interstitial peritubular tissue, arteries and arterioles are also affected, involvement of the capillaries makes them more permeable to albumin, causing a heavy proteinuria leading to the nephrotic syndrome.

**Q. The following conditions are particularly associated with the deposition of amyloid:**

- a) gas gangrene
- b) leprosy
- c) chronic osteomyelitis
- d) Type II diabetes
- e) pneumococcal pneumonia

Ans.

- a) False** Secondary amyloidosis is a feature of chronic rather than acute infections.
- b) True** Secondary amyloidosis is a frequent cause of death in lepromatous leprosy, resulting from the renal failure caused by the renal deposition of amyloid. In contrast amyloidosis is not a particular feature of tuberculoid leprosy.

- c) **True** Secondary amyloidosis occurs in chronic pyogenic osteomyelitis when the fibril is amyloid A (AA) and the related serum protein is serum amyloid A (SAA). AA amyloid is identical in all patients and is derived from the aminoterminal two thirds of an acute phase protein (SAA) which is synthesized in the liver as an apoprotein. SAA levels may increase a 1000 fold during an inflammatory response.
- d) **True** In Type II or non-insulin dependent diabetes amyloid consisting of a 37-aminoacid peptide known as amylin found in the islets. It has been suggested that the amyloid in this situation is secreted by the hyperfunctioning B cells in parallel with insulin. This type of diabetes is not the result of failure to secrete insulin but resistance on the part of the individual to the action of insulin, this resulting in constant hyperfunction of the B cells.
- e) **False** Acute pneumococcal pulmonary infections as with all acute infections do not lead to amyloidosis.

**Q. Secondary amyloidosis occurs in the following conditions:** (FCPS Surgery - July, 2008)

- a) familial Mediterranean fever
- b) thalassaemia
- c) sickle-cell disease
- d) multiple myeloma
- e) rheumatoid arthritis

Ans.

- a) **True** This is a rare genetic disorder largely restricted to Armenians, Sephardic Jews and other ethnic groups in the Middle East. Inheritance is normally autosomal recessive. Clinically the disease is characterized by recurring joint and abdominal pain and fever. It frequently presents in childhood and each attack may last 12–72 hours, but the attacks may be very intermittent. Amyloid fibrils biochemically resembling AA are deposited in the kidneys leading to proteinuria and finally renal failure.
- b) **False** This is a haemoglobinopathy occurring in the Mediterranean region. Amyloid does not develop but the condition is complicated by haemosiderosis and cirrhosis of the liver.
- c) **False** Sickle-cell disease is another haemoglobinopathy causing chronic anaemia. Attacks of ‘sickling’ may be precipitated by dehydration, chilling and infection. An attack is normally associated with severe pain. The complications include ulceration of the legs, respiratory infection, cardiomyopathy and thrombotic crises.
- d) **True** In multiple myeloma, renal involvement may be the result of the light chains (Bence-Jones) proteins, the light chains being toxic to the tubular epithelial cells or by the deposition of paraprotein either in the form of alpha or kappa light chain fragments in the blood vessels of the glomeruli and tubules resulting in renal failure. The most frequent paraprotein in multiple myeloma is a monoclonal IgG.
- e) **True** Rheumatoid arthritis has now replaced chronic pyogenic infection as the commonest cause of secondary amyloidosis. Postmortem examination reveals amyloid deposits in 20% of all cases. This disease is of unknown aetiology but with many immunological features including circulating IgM anti-immunoglobulin antibodies (the rheumatoid factor).

**Q. The essential constituents of primary amyloid include:**

- a) immunoglobulin
- b) complement
- c) albumin
- d) starch
- e) fibrils

Ans.

- a) **True** Two distinct types of amyloid are recognised, primary and secondary. In primary amyloidosis, the amyloid is derived from plasma cells and consists of AL protein made up of complete immunoglobulin light chains, the NH<sub>2</sub>-terminal fragments of light chains or both. In secondary amyloidosis, the amyloid protein (AA) does not have the structural homology to immunoglobulin, the AA fibrils are derived from a larger protein precursor in the serum called SAA (serum amyloid-associated protein) which is synthesized in the liver and circulates in association with a sub-group of

- lipoprotein. In both types, the major component of the fibrils (95%) is amyloid material and the remaining 5% is known as P component, which is a lycoprotein very similar in composition to a C-reactive protein (an acute phase reactant).
- b) False      The complement proteins are not components of amyloid.
- c) False      Albumin is not a component of amyloid.
- d) False      The term amyloid was first used by Virchow in 1842 because it stained violet with iodine after treatment with sulphuric acid, in the same way as starch. The most widely used stain for amyloid is Congo red which under ordinary light microscopy imparts a pinkish-red colour to the deposit. When observed by polarising microscopy, the deposits appear green.
- e) True      In all forms of amyloid, whether primary or secondary, the basic structure is that of non-branching fibrils of indefinite length and with a diameter of approximately 10 nm. X-ray crystallography demonstrates a characteristic cross pleated configuration regardless of the clinical condition or its chemical composition.

**Q. Amyloidosis may be associated with elevated levels of the following serum proteins:**

- a)  $\beta$ -lipoprotein
- b) SAA
- c) IgD
- d) M-protein
- e)  $\beta$ -microglobulin

Ans.

- a) False      Amyloidosis is not associated with elevated serum levels of  $\beta$ -lipoprotein. An elevation of these components occurs in a number of familial conditions and may lead to atherosclerosis with its attendant complications.
- b) True      SAA (serum amyloid-associated protein) circulates in association with HDL 3 subclass of lipoprotein. It is from SM that AA amyloid associated protein is derived, AA being a nonimmunoglobulin protein synthesized in the liver under the influence of cytokines. It is raised in all cases of secondary amyloidosis.
- c) False      IgD is present in low concentration in the serum. Increased levels of IgD may occur in chronic infections or in IgD myelomas.
- d) True      M protein is found in increased amounts in the serum of patients suffering from plasma cell neoplasms. The malignant B cells synthesize abnormal amounts of a single specific immunoglobulin (monoclonal gammopathy) producing an M (myeloma) protein spike on electrophoresis.
- e) False       $\beta_2$  microglobulin is a peptide which is a non-polymorphic protein in man which is a part of the HLA antigen.

**Q. Amyloid reacts with the following stains: (FCPS – Surgery - 09Ja)**

- a) thioflavine-T
- b) fluorescein isothiocyanate
- c) methyl violet
- d) methyl green
- e) Congo red

Ans.

- a) True      Thioflavine-T is a fluorochrome which reacts with amyloid. It is particularly useful for demonstrating small glomerular deposits.
- b) False      Fluorescein isothiocyanate does not stain amyloid deposits. It is used to conjugate with antibody in the fluorescent antibody technique.
- c) True      Methyl violet is a metachromatic stain, staining normal tissue violet and amyloid pink.
- d) False      Methyl green does not stain amyloid deposits. It reacts specifically with DNA and is used as part of the methyl green-pyronin stain (Unna-Pappenheim) which is specific for DNA and RNA.
- e) True      The Congo red test for amyloid depends on the specificity of this dye for amyloid. Intravenously administered Congo red disappears rapidly from the circulation in amyloid disease due to its rapid conjugation with this material. Amyloid material stained with Congo red can be seen to best advantage when the tissue is examined in polarised light when a green birefringence can be seen. Biopsy material to establish the presence of amyloid is usually taken from the rectum, gums or kidney.

## NEOPLASIA

### Basic components of neoplasm:

- Tumour parenchyma
- Reactive stroma- composed of connective tissue, blood vessels, cells of adaptive and innate immune system

### Some terms

- **Desmoplasia:** connective tissue stimulate abundant collagenous stroma, eg: schirrhous carcinoma of breast.
- **Papilloma:** benign epithelial neoplasm, microscopically or macroscopically visible finger like or warty projections from the epithelial surfaces, eg: large cystic masses in ovary called cysadenoma.
- **Polyp:** benign or malignant , macroscopically visible projections above the mucosal surface and projects, eg: gastric adenomatous polyp( composed of glandular structures).
- ✓ **Malignancy always raises a red flag**
- **Hamartomas:** disorganized growth, benign masses, composed of cells indigenous(native to the particular site) to the involved site, once it was thought that it was a developmental malformation.
- Many of the neoplasms have clonal chromosomal aberrations having acquired somatic mutations.
- **Choristoma:** heterotopic rest of cells. e.g: pancreatic tissue in the submucosa of the whole GIT.

## Benign & Malignant Tumours

### Classification of tumors on histological basis:

Tissue of Origin	Benign	Malignant	Tissue of Origin	Benign	Malignant
<b>Composed of one parenchymal cell type</b>					
Tumors of Mesenchymal Origin			Tumors of Epithelial Origin (cont'd)		
Connective tissue and derivatives	Fibroma Lipoma Chondroma Osteoma	Fibrosarcoma Liposarcoma Chondrosarcoma Osteogenic sarcoma	Epithelial lining of glands or ducts	Adenoma Papilloma Cystadenoma	Adenocarcinoma Papillary carcinomas Cystadenocarcinoma
Vessels and surface coverings			Respiratory passages	Bronchial adenoma	Bronchogenic carcinoma
Blood vessels	Hemangioma	Angiosarcoma	Renal epithelium	Renal tubular adenoma	Renal cell carcinoma
Lymph vessels	Lymphangioma	Lymphangiosarcoma	Liver cells	Hepatic adenoma	Hepatocellular carcinoma
Mesothelium	Benign fibrous tumor	Mesothelioma	Urinary tract epithelium (transitional)	Transitional cell papilloma	Transitional cell carcinoma
Brain coverings	Meningioma	Invasive meningioma	Placental epithelium	Hydatidiform mole	Choriocarcinoma
Blood Cells and Related Cells			Testicular epithelium (germ cells)		Seminoma Embryonal carcinoma
Hematopoietic cells		Leukemias	Tumors of Melanocytes	Nevus	Malignant melanoma
Lymphoid tissue		Lymphomas	<b>More than one neoplastic cell type—mixed tumors, usually derived from one germ cell layer</b>		
Muscle			Salivary glands	Pleomorphic adenoma (mixed tumor of salivary origin)	Malignant mixed tumor of salivary gland origin
Smooth	Leiomyoma	Leiomyosarcoma	Renal anlage		Wilms tumor
Striated	Rhabdomyoma	Rhabdomyosarcoma	<b>More than one neoplastic cell type derived from more than one germ cell layer—teratogenous</b>		
Tumors of Epithelial Origin			Totipotential cells in gonads or in embryonic rests	Mature teratoma, dermoid cyst	Immature teratoma, teratocarcinoma
Stratified squamous	Squamous cell papilloma	Squamous cell carcinoma			
Basal cells of skin or adnexa		Basal cell carcinoma			

(Ref: Robbins & Cotran-9<sup>th</sup>, P-268)

**Comparisons between Benign and Malignant Tumors:**

Characteristics	Benign	Malignant
<b>Differentiation/anaplasia</b>	Well differentiated; structure sometimes typical of tissue of origin	Some lack of differentiation (anaplasia); structure often atypical
<b>Rate of growth</b>	Usually progressive and slow; may come to a standstill or regress; mitotic figures rare and normal	Erratic and may be slow to rapid; mitotic figures may be numerous and abnormal
<b>Local invasion</b>	Usually cohesive expansile well-demarcated masses that do not invade or infiltrate surrounding normal tissues	Locally invasive, infiltrating surrounding tissue; sometimes may be seemingly cohesive and expansile
<b>Metastasis</b>	Absent	Frequently; more likely with large undifferentiated primary tumors

(Ref: Robbins+Cotran-9<sup>th</sup>, P-274)**KEY CONCEPTS****Characteristics of Benign and Malignant Neoplasms**

- Benign and malignant tumors can be distinguished from one another based on the degree of differentiation, rate of growth, local invasiveness, and distant spread.
- Benign tumors resemble the tissue of origin and are well differentiated; malignant tumors are less well differentiated or completely undifferentiated (anaplastic).
- Benign tumors are more likely to retain functions of their cells of origin, whereas malignant tumors sometimes acquire unexpected functions due to derangements in differentiation.
- Benign tumors are slow growing, while malignant tumors generally grow faster.
- Benign tumors are circumscribed and have a capsule; malignant tumors are poorly circumscribed and invade surrounding normal tissues.
- Benign tumors remain localized at the site of origin, whereas malignant tumors metastasize to distant sites.

**Question Bank**

**Q. Tumors that are benign in nature are (BSMMU – Non-Residency – MD, MS, Paediatrics, Basic Science – July '19)**

- melanoma
- seminoma
- dermatofibroma
- angiolipoma
- hepatoma

Ans. a) F (Malignant melanoma) b) F (Testicular germ cell tumour) c) T (Malignant counterpart is Dermatofibrosarcoma) d) T e) F (HCC)

(Ref: Robbins-9<sup>th</sup>, P-268)

**Q. Benign tumors are (BSMMU – Non-Residency – Dentistry – July '19)**

- a) melanoma
- b) mesothelioma
- c) fibroma
- d) lobular capillary hemangioma
- e) ameloblastoma

Ans. a) F (Malignant melanoma)    b) F (Malignant tumour of pleura, associated with asbestos, occupational cancer )    c) T    d) T    e) T

**Q. Hallmarks of malignant tumors are (BSMMU – Diploma - Dentistry – July '18)**

- a) anaplasia
- b) non-encapsulation
- c) increased number of mitosis
- d) local invasion
- e) metastasis

Ans. a) F    b) F    c) F    d) T    e) T

**Help Link:**

#### Cellular and Molecular Hallmarks of Cancer

- All cancers display 8 fundamental changes in cell physiology, which called hallmark of cancers
  1. Self-sufficiency in growth signals.
  2. Insensitivity to growth-inhibitory signals.
  3. Altered cellular metabolism
  4. Evasion of apoptosis. Tumors are resistant to programmed cell death.
  5. Limitless replicative potential (immortality)
  6. Sustained angiogenesis.
  7. Ability to invade and metastasize.
  8. Ability to evade the host immune response

**Q. Malignant tumors are (BSMMU – Non-Residency – MD, MS, Basic science – July' 18)**

- a) hamartoma
- b) hemangioma
- c) melanoma
- d) choristoma
- e) dysgerminoma

Ans. a) F    b) F    c) T    d) F    e) T

**Q. The following tumors are histologically benign (BSMMU – Non-Residency – MS, Basic Science – July' 17)**

- a) astrocytoma
- b) meningioma
- c) schwannoma
- d) medulloblastoma
- e) craniopharyngioma

Ans. a) F    b) T    c) T    d) F    e) T

**Q. Malignant tumours are (BSMMU – Diploma – Dentistry – July' 17)**

- a) adenoma
- b) fibro-sarcoma
- c) leiomyoma
- d) neurofibroma
- e) neuroblastoma

Ans. a) F    b) F    c) F    d) F    e) T

**Q. General phenomena that may be present with malignancy (BSMMU – Residency - Dentistry - March' 17)**

- a) fever
- b) cachexia
- c) thrombotic episodes
- d) polycythaemia
- e) dermatomyositis

**Ans.**

- a) **True** Fever, unassociated with infection, is particularly associated with the following tumours:
  - (a) Nephroblastoma
  - (b) Carcinoma of the renal tubules (hypernephroma)
  - (c) Lymphomata.
 The cause of such pyrexia remains uncertain although it must be due to pyrogens formed by the breakdown products of the tumour.
- b) **True** Cachexia is one of the common manifestations of widespread and terminal malignancy. The cause may be difficult to identify but in gastrointestinal tumours loss of appetite, bleeding and sepsis play a part.
- c) **True** The classic thrombotic episode associated with neoplasia is that described by Trousseau in 1865, of recurrent superficial and deep venous thrombosis which undergo spontaneous remission; thrombophlebitis migrans. Rarely, a non-bacterial thrombotic endocarditis occurs in Widespread malignant disease and even rarer is disseminated intravascular coagulation.
- d) **True** Polycythaemia does not normally complicate neoplasia, indeed the reverse is usually the case due either to blood loss, invasion of the red marrow or as yet unidentified causes. One exception is renal carcinoma which, by producing excessive erythropoietin, leads to a polycythaemia.
- e) **True** Dermatomyositis is a disorder which affects the skin, muscles and blood vessels. A coagulative necrosis occurs together with a small round cell infiltration around the smaller arteries. Approximately 30% of all patients suffering from dermatomyositis between 50 and 70 years of age are found to be suffering from disseminated malignant disease usually arising from the gastrointestinal tract and less frequently the bladder and bronchus.

(Ref: Smiddy)

**Help link:**

**Cancer cachexia:**

- Assoc with-
  - loss of fat and lean muscle,
  - elevated BMR,
  - evidence of systemic inflammation( increase in acute phase reactants).
  - Others: TNF- alpha (cachectin), proteolysis inducing factors.

**Q. Histologically benign tumours are (BSMMU – Residency - MS, Basic Science - March' 17)**

- a) astrocytoma
- b) meningioma
- c) schwannoma
- d) medulloblastoma
- e) craniopharyngioma

**Ans. a) F b) T c) T d) F e) T**

**Q. Benign tumors are (BSMMU –Residency – MS, Basic Science – March' 15)**

- a) astrocytoma
- b) meningioma
- c) schwannoma
- d) medulloblastoma
- e) craniopharyngioma

**Ans. a) F b) T (most meningioma are benign) c) T d) F e) T**

(Ref: Pathology outline.com)

**Q. The followings are examples of benign tumour:** (BSMMU - M. Phil, Diploma, July-09)

- a) Pleomorphic adenoma
- b) Mesothelioma
- c) Mature teratoma
- d) Seminoma
- e) Nevus

Ans. a) T (as well as locally malignant) b) F c) T d) F e) T

**Q. Hamartomas:** (BSMMU-MD/MS-06Ja)

- A. are composed of haphazardly arranged tissue
- B. contain immature tissue
- C. are precursors of teratoma
- D. are polyclonal
- E. gradually enlarge with body growth

Ans.

- a) T (*A mass of disorganized specialized tissues*) b) F (*Mature specialized cells or tissues*)  
c) F d) F e) F

**Q. An increase in the frequency of malignant disease occurs in the following conditions -** (BSMMU - M-Phil, Diploma, July-'05)

- |  |  |
|--|--|
| A. long term immunosuppressive therapy | T  |
| B. large bowel Crohn's disease         | F (According to Robbins, it is premalignant)     |
| C. coeliac disease                     | T (According to Robbins, it is not premalignant) |
| D. Ulcerative colitis                  | T  |
| E. xeroderma pigmentosum               | T  |

Ans.

**A. True** (Following homotransplantation, long term immunosuppressive therapy is required. In such patients continued suppression of the immune system leads to the development of lymphomas, most commonly immunoblastic B-cell lymphomas. Other types of tumour are rarely encountered.)

**B. False** (Malignant disease does not appear to follow long term granulomatous disease of the large bowel.)  
**True** (**Ref: Robbins-9<sup>th</sup>**)

**C. True** (In coeliac disease, otherwise known as gluten sensitive enteropathy, there is a long term risk of T-cell lymphomas development in the small bowel. The fundamental disorder is a sensitivity to gluten which contains the protein component of wheat known as gliadin. Large number of B cell sensitised to gliadin appear in the small bowel mucosa and biopsy shows marked atrophy and blunting of the villi, but increased mitotic activity in the crypts.)

**D. True** (Chronic ulcerative colitis is followed by an increase in large bowel malignancy. All recorded series show that the incidence of malignancy in this disease increases with the length of the clinical history and the severity of the disease.)

**E. True** (Xeroderma pigmentosum is a classical premalignant condition. Sufferers from this inherited disease rapidly develop skin cancer after exposure to ultra violet light.)

(**Ref: Smiddy**)

**Q. Hamartoma -** (BSMMU - M-Phil, Diploma, July-'05)

- |  |                |
|--|----------------|
| A. is a benign tumour                      | T              |
| B. is a tumour like malformation           | T              |
| C. is a mass of disorganized mature tissue | T              |
| D. arises from totipotential cells         | F              |
| E. is an ectopic rest of normal tissue     | F (choristoma) |

#### HELP LINK:

- Teratoma arises from totipotential cells.
- An ectopic rest of normal tissue is a feature of choristoma. Such as pancreatic cells under the mucosa of the small intestine.

**Q. Increased incidence of cancer has been observed:** (DMC - M. Phil, Diploma, July-05)

- |  |                                  |
|--|----------------------------------|
| a) Primary immuno deficiency state           | T                                |
| b) Immuno suppressed recipient of transplant | T                                |
| c) AIDS                                      | T (In HH8 caused Kaposi sarcoma) |
| d) Radiation and radio mimetic drugs         | T                                |
| e) Sarcoidosis                               | F                                |

**Q. A malignant tumor is characterized by -** (BSMMU – MD/MS - 05Ja)

- |   |   |
|---|---|
| a) cellular proliferation                                   | T |
| b) formation of a mass                                      | T |
| c) invasion of surrounding tissue                           | T |
| d) increased number of typical and atypical mitotic figures | T |
| e) metastasis   | T |

**Q. Neoplastic diseases may be associated with the following conditions:** (BSMMU – MD - 05Ja)

- A. Dermatomyositis
- B. Acanthosis nigricans
- C. Necrobiosis lipoidica (associated with DM)
- D. Thrombophlebitis migrans
- E. Polyarteritis nodosa

Ans.

- A. **True** (Approximately 20% of patients suffering from dermatomyositis have an underlying malignant condition. Dermatomyositis is an inflammatory lesion of muscle in which a mononuclear infiltrate occurs between the muscle bundles which themselves show mild degree of degeneration and a loss of the normal transverse striations. The cutaneous lesions consist of erythematous patches with slight oedema. The classic rash takes the form of a lilac or heliotrope discolouration of the upper eyelids accompanied by periorbital oedema. Clinically, there is muscle weakness.)
- B. **True** (Acanthosis nigricans is characterized by grey-black patches of verrucous hyperkeratosis. It is associated with visceral malignancy and occasionally with Hodgkin's disease or osteogenic sarcoma)
- C. **False** (Necrobiosis lipoidica is not associated with neoplasia. It is a condition in which yellowish demarcated lesions develop on the shins. Histologically the lesions may be necrobiotic and granulomatous. Diabetes is the underlying disease in approximately two third of affected individuals.)
- D. **True** (Thrombophlebitis migrans is chiefly associated with tumours of the pancreas, lung, stomach and female genital tract. Clinically, repeated attacks of segmental thrombosis occurs in both the superficial and the deep veins, attacks which heal spontaneously.)
- E. **False** (Polyarteritis nodosa is not associated with malignant disease but with hypersensitivity to a number of drugs including the sulphonamides and the anti- inflammatory agents such as phenylbutazone. It also occurs in HBV infections. The underlying cause is immune complex disease resulting in a necrotising arteritis affecting both deep and superficial vessels accompanied by polymorphonuclear leucocyte infiltration around the vessels.)

(Ref: Smiddy)

**Q. The following are malignant tumour:** (MD/MS (DMC)-05Ja)

- |                        |   |
|------------------------|---|
| a) Seminoma            | T |
| b) Melanoma            | T |
| c) Pleomorphic adenoma | F |
| d) Chondroma           | F |
| e) Carcinoid tumour    | T |

**HELP LINK:**

Ans. a) T b) F c) F d) F e) T

(Ref: Pathology outline.com)

**■ Classification tumors that arise from epithelial tissue:**

Tissue of origin	Benign tumour	Malignant tumour
Stratified squamous	Squamous cell papilloma	Squamous cell carcinoma
Basal cells of skin or adnexa	-	Basal cell carcinoma
Epithelial lining of glands or ducts	<ul style="list-style-type: none"> <li>• Adenoma</li> <li>• Papilloma</li> <li>• Cystadenoma</li> </ul>	<ul style="list-style-type: none"> <li>• Adenocarcinoma</li> <li>• Papillary carcinomas</li> <li>• Cystadeno-carcinoma</li> </ul>
Respiratory passages	Bronchial adenoma	Bronchogenic carcinoma
Renal epithelium	Renal tubular adenoma	Renal cell carcinoma
Liver cells	Liver cell adenoma	Hepatocellular carcinoma
Urinary tract epithelium (transitional)	Transitional cell papilloma	Transitional cell carcinoma
Placental epithelium	Hydatiform mole	Choriocarcinoma
Testicular epithelium (germ cells)	-	<ul style="list-style-type: none"> <li>• Seminoma</li> <li>• Embryonal carcinoma</li> </ul>
Tumors of melanocytes	Nevus	Malignant melanoma

(Ref: Robbins & Cotran-9<sup>th</sup>, P-268)**Q. Regarding tumors (M. phil, Diploma (DMC) – 03Ju, MD/MS (DMC)-01Ja)**

- a) Carcinoma of breast is the malignant proliferation of breast stroma F  
 b) Osteosarcoma is the malignant proliferation of bone marrow cells F  
 c) Familial retinoblastoma is the tumour of eye in elderly people F  
 d) Meningioma is the tumour of cerebral cortex F  
 e) Colonic carcinoma may present with large bowel obstruction T

**Q. Important changes seen in a malignant cell under microscope are - (BSMMU-MS-04Ja)**

- a) Irregularities in nuclear membrane T  
 b) Cytoplasmic vacuoles F  
 c) Large nucleolus T  
 d) Reduced nuclear cytoplasmic ratio F  
 e) Cytoplasmic inclusions F (Features of viral infection)

**Q. Following tumours are benign (M. phil, Diploma – 03Ju)**

- a) Chondroma T  
 b) Lymphoma F  
 c) Seminoma F  
 d) Leiomyoma T  
 e) Meningioma T

**Q. The following are benign tumours (BSMMU-MD/MS - 02Ja)**

- a) Choristoma  
 b) Pleomorphic adenoma  
 c) Mucoepidermoid tumour  
 d) Chondroma  
 e) Desmoid tumour

**Ans.**

- a) F (Ectopic rest of normal tissue)  
 b) T c) F d) T  
 e) F (Intermediate grade tumour lies between benign and malignant)

Help link:

Ameloblastoma

Neoplasm of odontogenic epithelium

The most common odontogenic neoplasm

(malignant villos as low as ngined glialgol T (a

smolealpolaris (a

nionlal cell clucionion (d

e) chondrocarcinoma

(b) Malignin's nfor

es (nsealpolos (a

**Q. Features that are more characteristic of benign tumours than malignant tumours include: (MD/MS (DMC) - 02Ja)**

- |                                       |   |
|---------------------------------------|---|
| a) Anaplasia                          | F |
| b) Capsule formation                  | T |
| c) Infiltration of surrounding tissue | F |
| d) Many mitotic figures               | F |
| e) Slow rate of growth.               | T |

**Q. Adenocarcinoma is the commonest type of primary malignant epithelial tumor to occur in the: (MD/MS (DMC)-02Ja)**

- |                    |         |
|--------------------|---------|
| a) Colon.          | T       |
| b) Lung.           | F (SCC) |
| c) Oesophagus.     | F (SCC) |
| d) Stomach.        | T       |
| e) Uterine cervix. | F       |

#### HELP LINK:

Arise from columnar cell/ gland.

**Sites:** breast, colon, stomach, kidney, gall bladder, endometrium, thyroid, pancreas.

**Q. Malignant cell is characterized by- (BSMMU-MS-01Ja)**

- |                               |   |
|-------------------------------|---|
| a) Abdominal size and shape   | T |
| b) Hyperchromasia             | T |
| c) Prominent nucleoli         | T |
| d) Abnormal mitotic figure    | T |
| e) Multinucleated giant cells | T |

## Locally malignant tumours

Locally malignant: tumours are those which show invasion but no metastasis. The term intermediate tumour is sometimes used for a tumour which behaves as benign. Locally malignant or even may show metastasis.

#### Examples:

1. **Basal cell carcinoma:** Local invasion occurs but rarely metastasize.
2. **Giant cell tumour of bone:** The tumour is classified as benign, but some are locally malignant and a small percentage shows metastasis.
3. **Ameloblastoma:** It arises from enamel organ. It is locally invasive but has a benign course in most cases.
4. **Carcinoid tumour:** It is classified as malignant. These tend to infiltrate locally and sometimes metastasize. Carcinoids of the appendix and rectum almost never metastasize.
5. **Gliomas:** Astrocytoma, oligodendrogloma and ependymoma. Distinction between benign and malignant lesions of gliomas is less evident. Most gliomas are highly invasive. Malignant gliomas very rarely metastasize outside the central nervous system.
6. **Deep-seated fibromatosis (Desmoid tumours):** These are infiltrative masses that do not metastasize.
7. **Mixed salivary tumours**

#### Question Bank

**Q. Locally malignant tumours are (BSMMU – Non-Residency – MS, Basic science – July' 18)**

- a) ameloblastoma
- b) basal cell carcinoma
- c) chondrosarcoma
- d) Marjolin's ulcer
- e) neuroblastoma

Ans.

- a) T (Biologically benign as well as locally malignant)

- b) T (also called Rodent ulcer)  
 c) F d) T e) F (Childhood small round cell tumour)

**Q. Locally malignant tumours are (BSMMU –Residency – MS, Basic Science – March' 15)**

- a) osteoclastoma
- b) Ewing's sarcoma
- c) Marjolin's ulcer
- d) rodent ulcer
- e) Paget's disease of the nipple

Ans.

- a) T (Giant cell tumour of bone)
- b) F (known as PNET when neuroectodermal differentiation is present)
- c) T d) T (BCC) e) F

**Q. Locally malignant conditions are (BSMMU –Non-Residency – MS, Basic science – July' 14)**

- a) Marjolin's ulcer
- b) melanoma
- c) giant cell tumour
- d) osteosarcoma
- e) rodent ulcer

Ans. a) T b) F c) T (of bone) d) F (primary malignant tumour of bone) e) T (BCC)

**Q. The following are locally malignant tumors: (DMC - M. Phil, Diploma, July-06)**

- |                                  |   |
|----------------------------------|---|
| a) neuroblastoma                 | F |
| b) choriocarcinoma               | F |
| c) mixed tumor of salivary gland | T |
| d) glioma                        | T |
| e) Burkitt's lymphoma            | F |

**Q. Locally malignant tumours: (BSMMU-05Ju)**

- |                                   |   |
|-----------------------------------|---|
| a. Pleomorphic adenoma            | T |
| b. Basal cell carcinoma           | T |
| c. Giant cell tumour              | T |
| d. Ameblastoma                    | T |
| e. Papillary carcinoma of thyroid | F |

#### Brain tumour

1. **Glioma (locally malignant tumour):** most common group of primary brain tumors, include astrocytomas, oligodendrogiomas, and ependymomas.
2. **Malignant:** medulloblastoma, Glioblastoma
3. **Meningioma:** predominantly benign.
4. **Other benign tumour:** neurofibroma, schwannoma.

#### Ameloblastoma

**Q. Ameloblastoma (BSMMU – Non-Residency – MS – July' 14)**

- a) is a locally malignant tumour
- b) occur in young adults
- c) contains enamel
- d) maxilla is the commonest site
- e) is a slow growing tumour

Ans. a) T b) T c) T d) F e) T

**Help link:**

**Ameloblastoma:**

- Neoplasm of odontogenic epithelium
- The most common odontogenic neoplasm

- Usually presents between ages 30 and 50
- Locally invasive but does not metastasise.
- Typically asymptomatic and appears as multilocular cyst radiographically.
- Most commonly forms in posterior mandible
- No ectomesenchymal differentiation
- Slow growing
- Has indolent (slow) course
- Treated by wide excision with a margin of normal tissue.
- Maxillary ameloblastoma can invade the cranial base and be lethal.

(Ref: Cawson's Oral pathology-8<sup>th</sup>; Robbins-9<sup>th</sup>)

**Q. Ameloblastoma- (BSMMU-MS-01Ja)**

- |   |   |
|---|---|
| a) Is neoplasm of odontogenic epithelium        | T |
| b) Is benign tumour                             | T |
| c) Usually occurs between ages of 30 – 50 years | T |
| d) Most commonly occurs in posterior mandible   | T |
| e) Typically appears as unilocular cyst.        | F |

### Tumours secreting hormone/ Hormone dependent tumours

11.9 Ectopic hormone production by tumours		
Hormone	Consequence	Tumours
<b>ADH</b>	<b>Hyponatraemia</b>	SCLC
<b>ACTH</b>	<b>Cushing's syndrome</b>	SCLC
<b>FGF-23</b>	<b>Hypophosphataemic osteomalacia</b>	Mesenchymal tumours
<b>Insulin</b>	<b>Hypoglycaemia</b>	Insulinoma
<b>Erythropoletin</b>	<b>Polycythaemia</b>	Kidney, hepatoma, cerebellar haemangioblastoma, uterine fibroids
<b>PTHRP</b>	<b>Hypercalcaemia</b>	NSCLC (squamous cell), breast, kidney

(ACTH = adrenocorticotrophic hormone; ADH = antidiuretic hormone; FGF = fibroblast growth factor; NSCLC = non-small cell lung cancer; PTHrP = parathyroid hormone-related protein; SCLC = small cell lung cancer)

**Q. Following malignancy(ies) is (are) hormone dependent (BSMMU-Residency - Basic science - March' 19)**

- a) papillary carcinoma of thyroid
- b) renal cell carcinoma
- c) carcinoma of breast
- d) carcinoma of pancreas
- e) carcinoma of prostate

Ans. a) T b) F c) T d) F

- e) **True** The scientific basis of hormone dependency was first established by Charles Huggins of Chicago after the Second World War when he discovered that carcinoma of the prostate was affected by altering its hormonal environment. Later he discovered that oophorectomy and adrenalectomy had a beneficial effect on disseminated breast cancer. It is interesting to note, however, that Beatson and others in the early part of this century had observed that the former operation sometimes produced great, although temporary, improvement in advanced breast cancer.

(Ref. Harsh Mohan pathology-7<sup>th</sup>, P-200)

**Q. The following tumors secretes hormone (BSMMU – Residency – MD, Basic science - March '17)**

- a) bronchial carcinoma
- b) choriocarcinoma
- c) carcinoid tumor
- d) craniopharyngioma
- e) myxoma

**Ans.** a) T b) T c) T d) F e) F

**Ans.**

**a) True** Bronchogenic carcinoma may secrete a variety of hormones producing thereby a number of paraneoplastic syndromes. The tumour like factors which maybe secreted include:

- (1) An antidiuretic hormone inducing hyponatraemia
- (2) Adrenocorticotrophic hormone causing Cushing's syndrome: this is the commonest hormonal manifestation
- (3) Parathyroid related hormone causing hypercalcaemia
- (4) Calcitonin causing hypocalcaemia
- (5) Gonadotrophins causing gynaecomastia in the male
- (6) Serotonin causing the carcinoid syndrome.

**b) True** Choriocarcinoma may be defined as a malignant tumour of trophoblastic origin. Most of these tumours are derived from gestational trophoblast and are a late complication of pregnancy. Non-gestational choriocarcinoma occasionally occurs, usually in the testes or in ovarian teratoma. Associated with pregnancy, approximately 50% arise in hydatidiform moles, 25% following abortions and 20% in a normal pregnancy. The tumours secrete chorionic gonadotrophin and in response to this stimulus ovarian cysts with luteinised theca interna are found in about one third of patients. The secretion of this hormone is an important feature, since failure of the level to fall to normal following treatment with chemotherapy indicates tumour is still present.

**c) True** Carcinoid tumours occur primarily in the gastrointestinal tract, most commonly in the ileum but they can in fact arise anywhere along the whole length of the gut and also in the bronchial tree, pancreas, biliary tree and ovary. The carcinoid syndrome, due to the secretion of 5HT (serotonin) arises in about 1% of all patients who develop a carcinoid whatever the primary site and in 20% of those in whom a gastrointestinal tumour develops associated with hepatic metastases. The importance of liver metastases is that serotonin is normally metabolized by the liver to an inactive end product 5-HIAA (5-hydroxyindole acetic acid). The release of 5HT causes intermittent flushing of the face, an increase in intestinal motility leading to diarrhoea and lesions on the pulmonary or tricuspid valves causing right sided heart failure.

**d) False**

**e) False**

(Ref: SMIDDY)

**Q. Hormone dependent tumour are (BSMMU – Residency – MS - March '17)**

- a) carcinoma of the prostate
- b) carcinoma of the breast
- c) papillary carcinoma of the thyroid
- d) osteogenic sarcoma
- e) bronchogenic carcinoma

**Ans.**

**a) True** The scientific basis of hormone dependency was first established by Charles Huggins of Chicago after the Second World War when he discovered that carcinoma of the prostate was affected by altering its hormonal environment. Later he discovered that oophorectomy and adrenalectomy had a beneficial effect on disseminated breast cancer. It is interesting to note, however, that Beatson and others in the early part of this century had observed that the former operation sometimes produced great, although temporary, improvement in advanced breast cancer.

**b) True**

- c) True  
d) False

e) False      Bronchial carcinomata are not hormone dependent although they occasionally produce hormones, in particular ACTH. When this occurs Cushingoid features develop.

**Q. Hormone sensitive tumors are (BSMMU – Non-Residency – MD, MS, Basic science, Dentistry – July' 16)**

- |  |   |
|--|---|
| a) adenocarcinoma of prostate            | T |
| b) gastrointestinal stromal tumor (GIST) | F |
| c) myxoma                                | F |
| d) carcinoma of breast                   | T |
| e) non small cell lung cancer (NSCLC)    | F |

**Q. Hormone producing tumors of the ovary are (BSMMU – Non-Residency – MD, MS, Basic science – July' 15)**

- |                         |   |
|-------------------------|---|
| a) hilus cell tumor     | F |
| b) struma ovarii        | T |
| c) dermoid cyst         | T |
| d) fibroma of ovary     | F |
| e) granulosa cell tumor | T |

**Q. Hormone dependent tumours are (BSMMU – Non-Residency – MS, Basic science – July' 14)**

- |                           |  |
|---------------------------|--|
| a) carcinoma prostate     |  |
| b) retinoblastoma         |  |
| c) bronchogenic carcinoma |  |
| d) neuroblastoma          |  |
| e) malignant melanoma     |  |

a) **True**      The scientific basis of hormone dependency was first established by Charles Huggins of Chicago after the Second World War when he discovered that carcinoma of the prostate was affected by altering its hormonal environment. Later he discovered that oophorectomy and adrenalectomy had a beneficial effect on disseminated breast cancer. It is interesting to note, however, that Beatson and others in the early part of this century had observed that the former operation sometimes produced great, although temporary, improvement in advanced breast cancer.

b) **False**      This is a tumour of infancy of which about 6% of cases are familial. There is no evidence of hormone dependency.

c) **False**      Bronchial carcinomata are not hormone dependent although they occasionally produce hormones, in particular ACTH. When this occurs Cushingoid features develop.

d) **False**

e) **True**      Although hormone therapy has no beneficial effect on malignant melanoma well documented reports do appear in the literature of such tumors regressing during pregnancy, presumably due to its hormonal effects.

(Ref: Smiddy)

**Q. Hormone related carcinoma include (BSMMU – Residency - MD – March' 14)**

- |                         |   |
|-------------------------|---|
| a) breast carcinoma     | T |
| b) thyroid carcinoma    | T |
| c) prostate carcinoma   | T |
| d) colorectal carcinoma | F |
| e) leukemia             | F |

**Q. Hormone secreting tumours are: (BSMMU – M. Phil, Diploma (Non-Residency)–March-2012, DMC & others – MD – March-2012)**

- |                            |   |
|----------------------------|---|
| a) gastric carcinoma       | F |
| b) malignant ovarian tumor | T |
| c) small cell lung cancer  | T |
| d) Wilm's tumor            | F |
| e) carcinoid tumor         | T |

**Q. The following tumours may produce hormone:** (BSMMU – M. Phil, Diploma (Non-Residency) – 11Ju, DMC & others – MD/MS – 11Ju)

- |                                   |   |
|-----------------------------------|---|
| a) Granulosa cell tumour of ovary | T |
| b) Fibroma of the ovary           | F |
| c) Choriocarcinoma                | T |
| d) Bronchial carcinoma            | T |
| e) Renal cell carcinoma           | T |

**Q. Erythropoietin producing tumours are:** (BSMMU – MD – January, 2010)

- |                              |   |
|------------------------------|---|
| a) renal carcinoma           | T |
| b) fibrosarcoma              | F |
| c) cerebellar haemangioma    | F |
| d) gastric carcinoma         | F |
| e) hepatocellular carcinoma. | T |

**HELP LINK:** Secondary causes of Polycythemia:

<b>Causes of increased erythropoietin</b>	
<b>Increased Epo due to tissue hypoxia</b>	<ul style="list-style-type: none"> <li>• High altitude</li> <li>• Lung disease</li> <li>• Cyanotic heart disease</li> <li>• High-affinity haemoglobins</li> </ul>
<b>Inappropriately increased Epo</b>	<p><b>Renal disease</b></p> <ul style="list-style-type: none"> <li>• Hydronephrosis</li> <li>• Cysts</li> <li>• Carcinoma</li> </ul> <p><b>Other tumours</b></p> <ul style="list-style-type: none"> <li>• Hepatoma</li> <li>• Bronchogenic carcinoma</li> <li>• Uterine fibroids</li> <li>• Phaeochromocytoma</li> <li>• Cerebellar haemangioblastoma.</li> </ul>

**Q. The following tumors may secrete hormones-** (BSMMU – MD - 05Ja)

- |                     |                             |
|---------------------|-----------------------------|
| A. Choriocarcinoma  | B. Bronchial carcinoma      |
| C. Carcinoid tumors | D. Benign teratoma of ovary |
| E. Ewing's sarcoma  |                             |

**Ans.**

- A. True** (HCG is found in choriocarcinoma, hydatidiform mole, teratocarcinoma of testis and ovarian carcinoma having chorionic tissue)
- B. True** (Bronchial carcinoma causes inappropriate ADH secretion causing hyponatraemia, ectopic ACTH secretion, PTH-related peptides causing hypercalcaemia)
- C. True** (It contains enterochromaffin cells which produce 5-HT, serotonin etc)
- D. False** (malignant teratoma can produce HCG)
- E. False** (it is a bone tumour. It does not produce hormone)

**HELP LINK:**

**■ Hormone producing tumor:**

Testis	Ovary
1. Leydig cell (Hilus cell tumor)	1. Sertoli, stroma cell tumor (Androblastoma)
2. Sertoli cell	2. Granulosa cell tumor
3. Granulosa cell	3. Choriocarcinoma
4. Choriocarcinoma	

**Q. The following are hormone dependant tumour:** (MD/MS (DMC)-05Ja)

- |                        |   |
|------------------------|---|
| a) Prostate tumor      | T |
| b) Ovarian tumour      | F |
| c) Thyroid             | T |
| d) Pituitary           | F |
| e) Cervix uteri tumour | F |

**Help link:** Others: Also breast carcinoma

## Differentiation and anaplasia

**Q. Features of malignancy are** (BSMMU –Residency - MD/MS, Basic science, Dentistry – March' 14)

- |                                    |   |
|------------------------------------|---|
| a) nuclear pleomorphism            | T |
| b) cytoplasmic vacuolation         | F |
| c) abnormal mitosis                | T |
| d) necrosis                        | F |
| e) foreign body type of giant cell | F |

**Help link:**

**Anaplasia:** Anaplasia means lack of differentiation.

(Ref: Robbins-9<sup>th</sup>, P-269)

**Characteristic features of anaplasia:**

- Pleomorphism:** Both the malignant cells and their nuclei characteristically display pleomorphism (i.e. variation in size and shape).
- Abnormal nuclear morphology:**
  - The nuclei are hyperchromatic and disproportionately large for the cell. The nucleus-to-cytoplasm ratio may approach 1: 1 instead of the normal 1 : 4 or 1 : 6.
  - The nuclear shape is also very variable.
- Mitoses:** Atypical, bizarre mitotic figures, sometimes producing tripolar, quadripolar or multipolar spindles.
- Loss of polarity:** Architecture, organization and orientation of malignant cells are markedly disturbed (i.e. they loss normal polarity).
- Other changes:** Formation of tumour giant cells having only a single huge polymorphic nucleus or two or more large hyperchromatic nuclei.

(Ref: Robbins-9<sup>th</sup>, P-270)

**Q. Regarding differentiation and anaplasia of a tumour:**

(BSMMU – Residency – MD/MS – March'13)

- Malignant tumours are never well differentiated
- Benign tumours may show features of anaplasia
- staging is dependant on the above factors
- Are assessed under microscope
- Are subjective assessment

Ans : a) F b) F c) F d) T e) T

**HELP LINK:**

**Differentiation:** Differentiation refers to the extent to which neoplastic parenchymal cells resemble the corresponding normal parenchymal cells, both morphologically and functionally. Well differentiated tumours are thus composed of cells resembling the mature normal cells of the tissue of origin of neoplasm. Malignant neoplasm range from well differentiated to undifferentiated.

(Ref: Robbins + Cotrans-9<sup>th</sup>, P-269-270)

## Dysplasia

**Q. Dysplasia (BSMMU – Non-Residency – Dentistry – July' 19)**

- a) involves the transformation of one mature cell type into another
- b) is a premalignant condition
- c) is associated with an increased cell number
- d) is associated with increased cell staining with hematoxylin
- e) is irreversible

Ans. a) F (it is called metaplasia) b) T (all dysplasia are premalignant) c) F (in hyperplasia, cell number increase) d) T e) F

### HELP LINK:

#### DYSPLASIA:

Dysplasia may be defined as disorderly non-neoplastic proliferation of either epithelial or rarely mesenchymal cells that have undergone atypical cytologic alteration involving cell e, shape and organization.

Dysplasia is particularly common in squamous and transitional epithelia such as—

- Cervix of uterus
- Respiratory tract in chronic cigarette smoker.
- Adjacent to foci of cancerous transformation
- Gall bladder (uncommon)
- Oral mucosa (uncommon)
- Skin
- Urinary bladder
- Larynx

#### Characteristics of dysplasia:

1. Dysplastic cells show considerable pleomorphism (variation in size and shape).
2. Hyperchromatic nuclei which are abnormally large for the size of cell.
3. Mitotic figures are more abundant than usual. Although almost invariably they conform to normal pattern.
4. Dyskeratosis and diminished cellular polarity.
5. Presence of koilocytosis, i.e. cytoplasmic vacuolation around the nucleus.

#### Clinical significance of dysplasia:

Dysplastic changes mild to moderate grade may transform to cancer but these changes are usually reversible and with the removal of inciting cause the epithelium may revert to normal. However severe dysplasia may be irreversible.

#### Dysplasia differs from cancer in two important respects:

- i) **Lack of invasiveness:** The abnormal cellular proliferation in dysplasia does not invade the basement membrane. Since the epithelium contains neither lymphatics nor blood vessels, the proliferating cells do not spread from the epithelium. However complete removal of dysplastic area is therefore curative, cancer in contrast, invades the basement membrane and spreads from the local (primary) site via lymphatics and blood vessels; so that excision of the local (primary) site may not be curative.
- ii) **Reversibility:** Dysplastic tissue, particularly that affected by the milder grades of dysplasia, may sometimes spontaneously return to normal- unlike cancer, which is an irreversible process. Severe dysplasia may be irreversible.

#### Diagnosis of dysplasia:

##### Gross examination:

Epithelial dysplasia including carcinoma *in situ* is usually asymptomatic and in many cases gross examination of the mucosa shows no abnormality. Dysplasia can sometimes be identified through special examination techniques (e.g. colposcopy for cervical dysplasia).

**Microscopic examination:**

The diagnosis of dysplasia is made by microscopic examination of sample from asymptomatic patients. Cytologic finding (in cells smears) must be confirmed by biopsy.

Microscopic examination of the nuclear and cytoplasmic features of dysplastic tissue provides evidence for both diagnosis and grading of dysplasia. The criteria for cytologic diagnosis of dysplasia are well established for the cervix uteri, urinary bladder, lung and uncommonly in gastrointestinal tract and breast.

**Q. Dysplasia (BSMMU – Residency – MD, MS, Basic science, Dentistry – March' 16)**

- |   |   |
|---|---|
| a) literally means disordered to cancer               | T |
| b) necessarily progresses to cancer                   | F |
| c) is encountered mostly in connective tissue         | F |
| d) is often found adjacent to foci of invasive cancer | T |
| e) exhibits pleomorphism                              | T |

**Q. Dysplasia (BSMMU – Non-Residency – March' 13, 12; Residency – 11Ja)**

- |   |   |
|---|---|
| a) literally means disordered growth            | T |
| b) may be reversible                            | T |
| c) always progress to cancer                    | F |
| d) is encountered only in connective tissue     | F |
| e) is found adjacent to foci of invasive cancer | T |

**Help link:****Regarding dysplasia and metaplasia:**

- Metaplasia means replacement of one type of cells with another type of cells but not phenotypically change, assoc. with tissue damage, repair, and regeneration.
- Dysplasia:

Cervical intraepithelial neoplasia (CIN-1): when dysplastic epithelium is present in basal one third.

CIN-2: basal two third is dysplastic

CIN-3: Whole epithelium is dysplastic but no crossing the basement membrane.

- If crossing the basement membrane, then it is called invasive carcinoma.
- Mutations assoc with cancers may have mild dysplasia.
- It may be precursors of malignant neoplasm, but not always progress to cancer
- It is always completely reversible, if inciting agents are withdrawn.
- It often occurs in metaplastic epithelium, but all metaplastic epithelium is not dysplastic.

**Q. Dysplasia is characterized by the following features - (MD/MS (DMC) – January, 2010)**

- |  |   |
|--|---|
| a. evidence of decreased growth        | F |
| b. absence of cellular atypia          | F |
| c. loss of epithelial polarity         | T |
| d. increased number of mitotic figures | T |
| e. low nuclear cytoplasmic ratio       | F |

**HELP LINK:**

Dysplasia means disordered growth which is characterized by a loss in the uniformity of the individual cells as well as a loss in their architectural orientation. It is encountered principally in the epithelia.

**■ Criteria:**

- The dysplastic cells exhibit pleomorphism.
- Hyperchromatic nuclei.
- Abundant mitotic figures.

**■ Sites:**

- Epidermis of skin
- Epithelium of respiratory tract.

■ Difference between metaplasia & dysplasia

Metaplasia	Dysplasia
1. Metaplasia is a reversible change in which one adult cell type (epithelial or mesothelial) is replaced by another adult cell type.	1. A loss in the uniformity of the individual cells as well as a loss in their architectural orientation.
2. It occurs both in epithelium and mesenchyme.	2. It occurs mostly in epithelium.

Q. Following features describe dysplasia: (BSMMU – MD – January, 2010)

- |  |   |
|--|---|
| a) an increase in epithelial thickness | T |
| b) loss of maturation of cells         | F |
| c) loss of orientation of cells        | T |
| d) loss of cohesion of cells           | F |
| e) Intact basement membrane            | T |

Q. Dysplastic epithelium (M. phil, Diploma (DMC) – 03Ju)

- |  |   |
|--|---|
| a) Invariably becomes neoplastic             | F |
| b) Characteristically shows lack of polarity | T |
| c) May show nuclear pleomorphism             | T |
| d) May occur in metaplastic epithelium       | T |
| e) In the cervix may be detected by a smear  | T |

Q. Dysplastic epithelium: (MD/MS (DMC)-01Ja)

- |   |   |
|---|---|
| A. Invariably becomes neoplastic.             | F |
| B. Characteristically shows lack of polarity. | T |
| C. May show nuclear pleomorphism.             | T |
| D. May occur in metaplastic epithelium.       | T |
| E. In the cervix may be detected by a smear.  | T |

## METASTASIS

■ **Metastasis:** It is the process whereby primary malignant tumor spread to form secondary tumor at a distant site discontinuous with the primary tumor.

[All malignant tumor metastasize except tumor of brain 'glioma' and basal cell carcinoma of skin.]

■ **Methods of metastasis:**

1. Seeding of body cavities and surface
2. Lymphatic spread.
3. Hematogenous spread

1. **Seeding of body cavities and surface:** It occurs whenever a malignant neoplasm penetrates into a natural "open field". It involves the peritoneal cavity (most often), pleural, pericardial, subarachnoid and joint spaces. e.g.

- Transperitoneal implantation - Ca stomach, Ca colon, Ca ovary
- Transpleural implantation - Ca lung
- Transpericardial implantation - Ca bronchus
- Sometimes mucus-secreting appendiceal carcinomas fill the peritoneal cavity with a gelatinous neoplastic mass referred to as *pseudomyxoma peritonei*.

2. **Lymphatic spread:** Common pathway for initial dissemination of carcinoma, and sarcomas may also use it. The pattern of lymph node involvement follows the natural routes of lymphatic drainage. e.g.

- Carcinomas of the breast usually arise in the upper outer quadrants, they generally disseminate first to the axillary lymph nodes. Cancers of the inner quadrants drain to the nodes along the internal mammary arteries. Thereafter the infraclavicular and supraclavicular nodes may become involved.

- Carcinomas of the lung arising in the major respiratory passages metastasize first to the perihilar tracheobronchial and mediastinal nodes. Local lymph nodes, however, may be bypassed—so-called “skip metastasis”—because of venous-lymphatic anastomoses or because inflammation or radiation has obliterated lymphatic channels.

**3. Haematogenous spread:** It is typical of sarcomas but is also seen with carcinomas. Arteries, with their thicker walls, are less readily penetrated than are veins.

a. **Venous spread:** With venous invasion the blood-borne cells follow the venous flow draining the site of the neoplasm, and the tumor cells often come to rest in the first capillary bed they encounter. Liver and lungs are most frequently involved in such hematogenous dissemination.

- Invasion → embolism → Portal & systemic circulation → tumor embolism to liver.
  - Invasion → embolism → systemic circulation → tumor embolism to lungs.
  - Cancers arising in close proximity to the vertebral column often embolize through the paravertebral plexus, and this pathway is involved in the frequent vertebral metastases of carcinomas of the thyroid and prostate.
- Certain cancers have a propensity for invasion of veins. e.g.
- Renal cell carcinoma → branches of renal vein → renal vein → Inferior vena cava → sometimes Rt. side of heart.
  - Hepatocellular carcinoma → portal & hepatic vein → Main venous channel.

b. **Arterial spread:** Arterial spread may occur when tumor cells pass through the pulmonary capillary beds or pulmonary arteriovenous shunts or when pulmonary metastases themselves give rise to additional tumor emboli.

(Ref: Robbins+Cotran-9<sup>th</sup>, P-273-274)

#### Box: Metastasis

- 30% of newly diagnosed solid tumours (except melanoma) present with metastasis.
- Lymphatic route:** mostly carcinoma but sometimes sarcoma.
- Hematogenous route:** typically sarcoma but sometimes carcinoma.
- Skip metastasis:** when local lymph nodes are bypassed because venous-lymphatic anastomoses or inflammation or radiation.
- Sentinel lymph node:** first lymph node that receives lymph flow from the primary tumour.
- Blood borne metastasis commonly occurs in lungs and liver

#### No metastasis:

- Basal cell carcinoma
- Glial cell carcinoma
- Giant cell tumour of bone
- Ameloblastoma
- Craniopharyngioma
- Carcinoid tumour
- Gliomas
- Deep seated fibromatosis

#### Bony or osseous metastasis are common in carcinoma of

- Breast
- Bronchus or lungs
- Thyroid
- Prostate
- Kidney

The following tumours commonly metastasize to bone:

1. Breast carcinoma
2. Carcinoma of Bronchus or lungs
3. Thyroid carcinoma
4. Carcinoma of Prostate
5. Renal tumour

\* All malignant tumours metastasize except basal cell carcinoma & glial cell tumour.

\* Benign tumours do not metastasize.

Name of the cancers	Where metastasis
Carcinoma of thyroid and prostate	Vertebral metastasis
RCC	the renal veins look like snake like fascion upto IVC to right heart.
Breast carcinoma, thyroid, kidney, lung, prostate	bone,
Lung carcinoma	Brain, liver, adrenal gland and, bone, (memo-BLAB)
Neuroblastoma(PNET/Ewing sarcoma)	liver and bones
Skeletal muscle and spleen has a high cardiac output and large vascular beds but	rarely metastasis.
Gastric carcinoma	Lung, liver, bone marrow, peritoneum
Skin	Breast, lung, ovary, colon, kidney(memo- BLOCK)

- Lung is the site where metastasis from: breast, colon, tumours of head and neck
- Liver is the site comes from: colorectal cancer, ocular melanoma, neuroendocrine tumour.
- Brain is the site from: lung, breast, melanoma, colon, unknown primary, thyroid (follicular carcinoma.)
- Most common tumours in men: prostate, lung, colon, rectum, stomach, liver
- Most common tumours in women: breast, lung, colon, rectum, cervix
- Race is an important risk for certain cancers
- Precursor lesions can cause localized morphological changes lead to high risk of cancer.

#### Question Bank

**Q. Malignant tumors spread by (BSMMU – Non-Residency – MD, MS, Paediatrics, Basic Science – July’, Dentistry 19)**

- a) lymphatics
- b) transcelomic seedling
- c) cerebrospinal fluid
- d) urine
- e) lacrimal secretion

Ans. a) T   b) T   c) T   d) F   e) F

(Ref: Robbins-9<sup>th</sup>, P-272)

**Q.7. Malignant tumors can spread by (BSMMU – Non-Residency – Dentistry – July’ 19)**

- a) lymphatics
- b) transcelomic seedling
- c) cerebrospinal fluid
- d) saliva
- e) lacrimal secretion

Ans. a) T   b) T   c) T   d) F   e) F

**Q. Primary tumor site(s) that metastasize(s) to the brain include(s) (BSMMU – Non-Residency – MD, Basic Science – July' 18)**

- a) lung
- b) breast
- c) heart
- d) spleen
- e) colon

Ans. a) T b) T c) F d) F e) T

**Help Link:**

Five primary tumours account for 80% of brain metastases :

- Lung cancer
- Renal cell carcinoma (single foci)
- Breast cancer (Single foci)
- Melanoma (multiple foci)
- Gastrointestinal tract adenocarcinomas (the majority colorectal carcinoma)(Single foci)

**Q. Malignant tumours metastasize to bones are (BSMMU – Non-Residency – MS, Basic science – July' 18)**

- a) seminoma of testes
- b) follicular carcinoma of the thyroid
- c) carcinoma of the prostate
- d) renal cell carcinoma
- e) carcinoma of the gall bladder

Ans. a) F b) T c) T d) T e) F

**Q. Tumors presenting with early metastasis are - (BSMMU – Non-Residency – MD, MS, Basic Science & Dentistry – July' 17)**

- a) pancreatic carcinoma
- b) spermatocytic seminoma
- c) ameloblastoma
- d) embryonal carcinoma
- e) Bowen's disease

Ans.

- a) T ( 85% have extension beyond pancreas at diagnosis)
- b) F (does not produce metastasis, prognosis is excellent)
- c) F (slow growing, rarely metastasis)
- d) T (One fifth to two thirds of patients with tumours composed predominantly of embryonal carcinoma have metastases at diagnosis)
- e) F (premalignant condition of skin)

**Q. Bony metastases common in carcinoma of (BSMMU – Non-Residency – MD, MS, Basic science, Dentistry – July' 16)**

- |             |   |
|-------------|---|
| a) stomach  | F |
| b) breast   | T |
| c) kidney   | T |
| d) prostate | T |
| e) brain    | F |

**Q. Metastasis in a lymph node (BSMMU – Residency – MD, MS, Basic science, Dentistry – March' 16)**

- a) is more common in carcinomas than in sarcomas
- b) is a prerequisite for tumour staging
- c) is not possible to detect by FNAC
- d) first occurs in medullary sinuses
- e) is the surest evidence of malignancy

④ Primary sites from where metastasis in skeletal system occurs (BSMMU –Residency – Basic Science – March' 15)

- a) breast
- b) thyroid
- c) ovary
- d) bladder
- e) kidney

Ans. a) T b) T c) F d) F e) T

④ Malignant tumours frequently metastasize to bone are (BSMMU –Residency – MD, MS, Basic – March' 15; MD/MS (Residency) – January, 2011)

- a) papillary carcinoma of thyroid
- b) renal cell carcinoma
- c) adenocarcinoma of prostate
- d) ductal carcinoma of breast
- e) malignant melanoma of skin

Ans. a) F b) T c) T d) T e) F

④ Tumors commonly metastasize to the bone include (BSMMU –Residency – MD, Basic science – March' 14)

- |                                   |   |
|-----------------------------------|---|
| a) seminoma of testis             | F |
| b) papillary carcinoma of thyroid | F |
| c) renal cell carcinoma           | T |
| d) adenocarcinoma of gall bladder | F |
| e) adenocarcinoma of prostate     | T |

④ The following tumours commonly metastasize to bone (BSMMU–Non-Residency-MD/MS, Basic science–13Ju)

- |                                   |   |
|-----------------------------------|---|
| a) papillary carcinoma of thyroid | F |
| b) renal cell carcinoma           | T |
| c) malignant melanoma of skin     | F |
| d) adenocarcinoma of prostate     | T |
| e) seminoma                       | F |

④ Common primary source of a metastatic bone tumour are: (BSMMU - M. Thil, Diploma, July-'09)

- |                |   |
|----------------|---|
| a) Breast      | T |
| b) Testis      | F |
| c) Prostate    | T |
| d) Kidney      | T |
| e) Nasopharynx | F |

④ Malignant tumours of the following organs commonly metastasized to bone: (BSMMU – MD/MS - January, 2009)

- |                                   |   |
|-----------------------------------|---|
| a) seminoma of testis             | F |
| b) gall bladder adenocarcinoma    | F |
| c) papillary carcinoma of thyroid | F |
| d) renal cell carcinoma           | T |
| e) adenocarcinoma of prostate     | T |

④ The following tumours commonly metastasize to bone: (BSMMU – MD/MS - January, 2008)

- |                                    |   |
|------------------------------------|---|
| a) carcinoma of cervix             | F |
| b) follicular carcinoma of thyroid | T |
| c) adenocarcinoma of prostate      | T |
| d) seminoma of testis              | F |
| e) Wilms tumour of kidney          | T |

**Q. Metastatic carcinoma occurs in:** (DMC - M. Phil, Diploma, July-07)

- |                                   |   |
|-----------------------------------|---|
| a) kidney                         | T |
| b) the wall of inferior vena cava | T |
| c) old tuberculus lesion          | F |
| d) brain                          | T |
| e) cornea                         | F |

**Q. Calcified metastasis occurs in the lungs from the following organs:** (BSMMU-MS-07Ja)

- |            |                      |
|------------|----------------------|
| a) Stomach | T                    |
| b) Testis  | T                    |
| c) Breast  | T                    |
| d) Ovary   | T                    |
| e) Thyroid | T (& kidney, uterus) |

**Q. Metastasis in lymph nodes is a common feature of –** (BSMMU-07Ja)

- |                            |   |
|----------------------------|---|
| a. Basal cell carcinoma    | F |
| b. Fibroadenoma            | F |
| c. Malignant melanoma      | T |
| d. Seminoma                | T |
| e. Squamous cell carcinoma | T |

**Q. Metastasis of malignant tumours in lymph nodes -** (BSMMU - M-Phil, Diploma, July-'06)

- |  |   |
|--|---|
| a) Is common sarcomas  | F |
| b) Generally follows the route of lymphatic drainage                   | T |
| c) Is always present when lymph nodes are more than one cm in diameter | F |
| d) Can be detected by fine needle aspiration cytology                  | T |
| e) influence staging   | T |

**Q. Metastases in lymph nodes are common features of:** (MD/MS (DMC)-02Ja)

- |                            |   |
|----------------------------|---|
| A. Basal cell carcinoma    | F |
| B. Fibroadenoma            | F |
| C. Malignant melanoma      | T |
| D. Seminoma                | T |
| E. Squamous cell carcinoma | T |

**Q. Blood borne metastases are a common feature of:** (MD/MS (DMC)-02Ja)

- |   |   |
|---|---|
| a) Astrocytoma.                           | F |
| b) Basal cell carcinoma.                  | F |
| c) Osteosarcoma.                          | T |
| d) Prostatic carcinoma.                   | T |
| e) Squamous cell carcinoma of the tongue. | F |

### Tumour angiogenesis

**Q. Angiogenesis in tumour is promoted by the following factors -** (BSMMU - M-Phil, Diploma, July-'06)

- |                                       |   |
|---------------------------------------|---|
| a) Vascular endothelial growth factor | T |
| b) Hypoxia inducible factor           | T |
| c) Thrombospondin                     | F |
| d) Basic fibroblast growth factor     | T |
| e) Endostatin                         | F |

**HELP LINK:** Angiogenesis is induced mainly by –

**Angiogenesis:**

- Process of new blood vessels formation
- Induced by:

- Hypoxia inducible factors
- vascular endothelial growth factor (VEGF)
- Angiopoietine 1 (Ang 1)
- Basic fibroblast growth factor (bFGF)
- PDGF and TGF- $\beta$ .

- **Basic mechanisms:**

sprouting of new vessels from the existing one, helped by NO, VEGF, bFGF, Recruitment of periendothelial cells,

- **Process of angiogenesis involves:** Signaling pathways:- cell-cell interactions, ECM proteins, tissue enzymes, Some GFs, Notch pathways, ECM proteins, enzymes.

## Proto-oncogene

**Proto-oncogene:**

The unmutated cellular counterparts of oncogenes are called **proto-oncogenes**.

(Ref: Robbins+Cotran-9<sup>th</sup>, P-284)

Or,

Proto-oncogenes are cellular genes that promote normal growth and differentiation.

**Role of proto-oncogene in tumour development:** Proto-oncogene may be converted into cellular oncogenes (c-ons) by point mutation or chromosomal rearrangement, chemical carcinogen, radiation or oncogenic viruses that are involved in tumour development.

**Example:**

Protooncogene	Associated tumour
TGF - $\alpha$	Hepatocellular carcinoma
SIS (official name PBGFB)	Astrocytoma Osteosarcoma
HST1	Stomach cancer
INT2 (official name FGF3)	Bladder cancer Breast cancer Melanoma
TGFA	Astrocytomas Hepatocellular carcinomas
HGF	Thyroid cancer
PDGF-R	Gliomas
HST-1	Stomach cancer
ABL	Chronic myeloid leukaemia

(Ref: Robbins+Cotran-9<sup>th</sup>, P-284)

## Oncogenes

**Oncogenes, Oncoproteins, and Unregulated Cell Proliferation:**

- **Proto-oncogenes:** normal cellular genes whose products promote cell proliferation
- **Oncogenes:** mutated or overexpressed versions of proto-oncogenes that function autonomously, having lost dependence on normal growth promoting signals
- **Oncoprotein:** a protein encoded by an oncogene that drives increased cell proliferation through one of several mechanisms

**What are the proto-oncogens changed to oncogen and leads to cancer?**

- PDGF-beta- astrocytoma
- FGF- osteosarcoma, stomach, UB, breast, melanoma
- TGF-alpha- astrocytoma
- HGF- HCC, thyroid cancer

- KRAS- colon, lung, pancreas
- ABL- CML
- Myc- burkitt's lymphoma

### Question Bank

**Q. Oncogenes (BSMMU – Residency – MD, MS, Basic science, Dentistry – March' 16)**

- a) have the ability to promote cell growth in the absence of mitogenic signals
- b) promote autonomous cell growth in cancer cells
- c) product are called oncoproteins
- d) are physiologic regulators of cell proliferation and differentiation
- e) are biochemical indicators of the presence of a tumour

Ans. a) T b) T c) T d) F e) F

#### Help link:

Genes that promote autonomous cell growth in cancer cells are called **oncogenes**. Or,

**Oncogenes** are the cancer causing genes which are derived from proto-oncogenes.

#### Functions:

1. It inactivates/ suppresses the action of cancer suppressor gene, thus causing tumour formation.
2. It causes abnormal growth and differentiation of cells, thus causing tumour formation.

(Ref: Prof. Khaleque; Robbins+Cotran-9<sup>th</sup>, P-284)

**Q. Regarding p53 gene:** (BSMMU – M. Phil, Diploma (Non-Residency)–March-2012, DMC & others – MD/MS – March-2012)

- a) it is associated with adult malignant tumours only
- b) it arrests cell cycle in G1 phase
- c) it is stimulated by ionizing radiation
- d) it is located in chromosome 21
- e) it is a tumour suppressor gene

Ans. a) F b) T c) T d) F e) T

**HELP LINK:** p53 gene is located on chromosome 17p 13.1. and is the most common, target for genetic alterations found in human cancers. A little over 50% of human tumors contain mutations in this gene.

p53-links cell damage with DNA repair, cell cycle arrest and apoptosis. In response to DNA damage,-it is phosphorylated by genes that sense the damage and are involved in DNA repair. p53 assists in DNA repair by causing G1 arrest and inducing DNA repair genes.

A cell with damaged DNA that cannot be repaired is directed by p53 to undergo apoptosis. So, p53 is called 'guardian of the genome'.

With homozygous loss of p53, DNA damage goes unrepaired, mutations become fixed in dividing cells, and the cells turn into a one-way street leading to malignant transformation.

**Q. p53 gene, designated as guardian of the genome:** (BSMMU – MD – January, 2010)

- a) is found in more than 50% human tumours
- b) is a tumour suppressor gene
- c) is down regulated following DNA damage of the cells
- d) produces tumour when one allele is lost
- e) triggers apoptosis in damaged cell

Ans.

a) T b) T c) F (upregulated) d) F( both allele should lost becoz it is a tumour suppressor gene) e) T

(Ref. Robbins-9<sup>th</sup>, P-293-294)

#### HELP LINK:

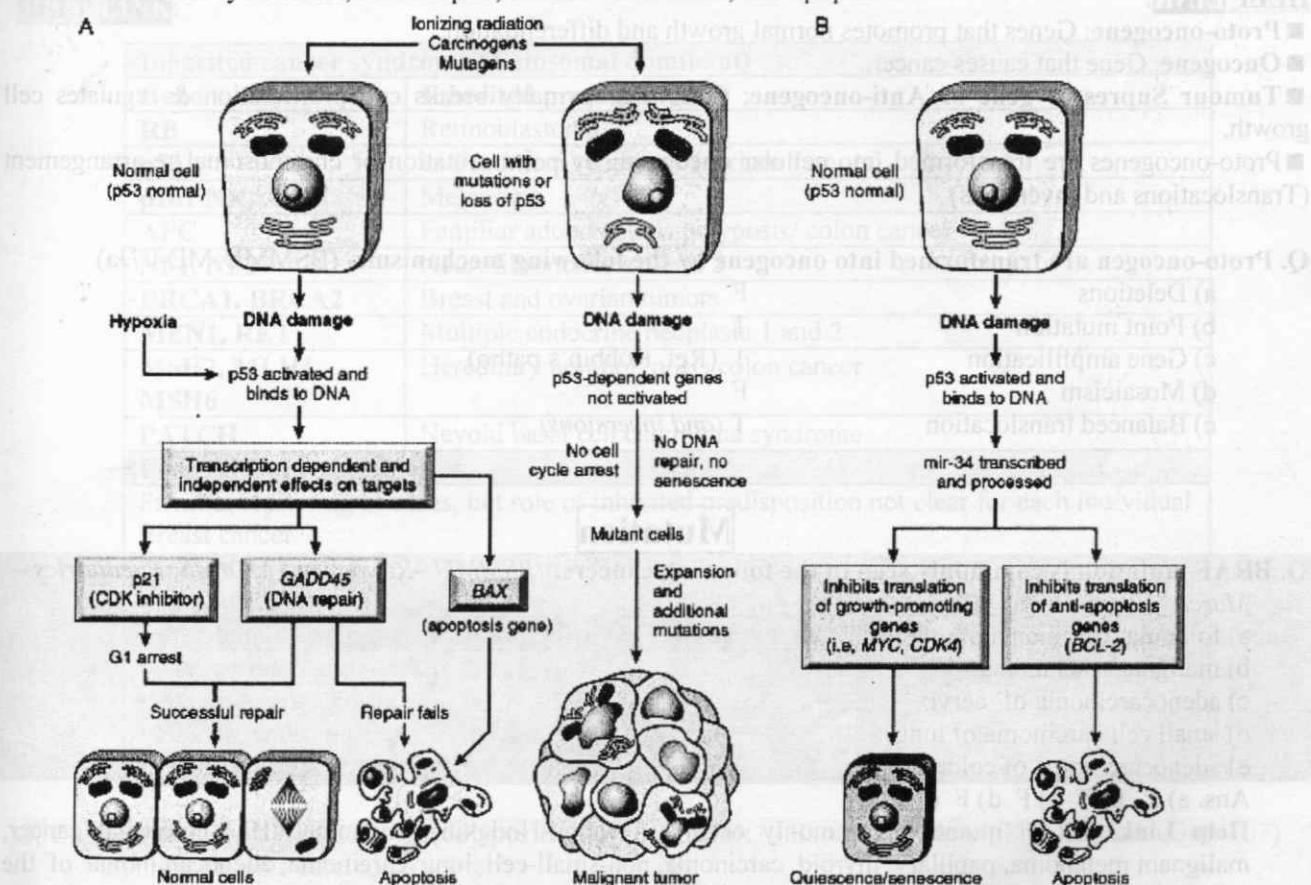
#### Tp53: Guardian of the Genome.

TP53, a tumor suppressor gene that regulates cell cycle progression, DNA repair, cellular senescence, and apoptosis, is the most frequently mutated gene in human cancers. Loss-of-function mutations in TP53, located on chromosome 17p13.1, are found in more than 50% of cancers. Moreover, TP53 mutations occur with some frequency in virtually every type of cancer, including carcinomas of the lung, colon, and breast—the three leading causes of cancer death. In most cases, mutations are present in both TP53 alleles and are acquired in somatic cells

(not inherited in the germline) Less commonly, individuals inherit one mutated TP53 allele. As in the case of the RB tumor suppressor and retinoblastoma, inheritance of a mutated copy of TP53 predisposes individuals to malignant tumors because only one additional "hit" in the lone normal allele is needed to abrogate TP53 function. Such individuals, said to have the Li-Fraumeni syndrome, have a 25-fold greater chance of

developing a malignant tumor by age 50 than the general population. In contrast to individuals who inherit a mutant RB allele, the spectrum of tumors that develop in persons with the Li-Fraumeni syndrome is quite varied; the most common types of tumors are sarcomas, breast cancer, leukemias, brain tumors, and carcinomas of the adrenal cortex. People with the Li-Fraumeni syndrome often develop cancer at younger ages and are more likely to suffer from multiple primary tumors of varying types than are normal individuals.

- The p53 protein is the central monitor of stress in the cell and can be activated by anoxia, inappropriate signaling by mutated oncogenes, or DNA damage. p53 controls the expression and activity of proteins involved in cell cycle arrest, DNA repair, cellular senescence, and apoptosis.



**FIGURE:** A, The role of p53 in maintaining the integrity of the genome. Activation of normal p53 by DNA-damaging agents or by hypoxia leads to cell cycle arrest in G<sub>1</sub> and induction of DNA repair, by transcriptional up-regulation of the cyclin-dependent kinase inhibitor CDKN1A (p21) and the GADD45 genes. Successful repair of DNA allows cells to proceed with the cell cycle; if DNA repair fails, p53 triggers either apoptosis or senescence. In cells with loss or mutations of p53, DNA damage does not induce cell cycle arrest or DNA repair, and genetically damaged cells proliferate, giving rise eventually to malignant neoplasms. B, p53 mediates gene repression by activating transcription of miRNAs. p53 activates transcription of the miR34 family of miRNAs. miR34s repress translation of both proliferative genes.

- DNA damage is sensed by complexes containing kinases of the ATM/ATR family; these kinases phosphorylate p53, liberating it from inhibitors such as MDM2. Active p53 then upregulates the expression of proteins such as the cyclin-dependent kinase inhibitor p21, thereby causing cell-cycle arrest at the G1-S checkpoint. This pause allows cells to repair DNA damage.

- If DNA damage cannot be repaired, p53 induces additional events that lead to cellular senescence or apoptosis.
- The majority of human cancers demonstrate biallelic loss-of-function mutations in TP53. Rare patients with Li-Fraumeni syndrome inherit one defective copy of TP53 and have a very high incidence of a wide variety of cancers.
- Like RB, p53 is inactivated by viral oncoproteins, such as the E6 protein of HPV.

(Ref: Robbins & Cotran-9th, P-296-297)

**Q. Proto-oncogenes:** (BSMMU - M. Phil, Diploma-07July)

- |  |   |
|--|---|
| a) are carcinogenic retroviruses                 | F |
| b) are only expressed in malignant tissues       | F |
| c) control cell growth and differentiation       | T |
| d) are transiently upregulated by growth factors | T |
| e) inactivate oncogenes                          | F |

**HELP LINK:**

■ **Proto-oncogene:** Genes that promotes normal growth and differentiation.

■ **Oncogene:** Gene that causes cancer.

■ **Tumour Suppressor gene or Anti-oncogene:** Gene that normally breaks cell proliferation & regulates cell growth.

■ Proto-oncogenes are transformed into cellular oncogenes by point mutation or chromosomal re-arrangement (Translocations and inversions)

**Q. Proto-oncogenes are transformed into oncogene by the following mechanisms-** (BSMMU-MD-07Ja)

- |                           |                         |
|---------------------------|-------------------------|
| a) Deletions              | F                       |
| b) Point mutation         | T                       |
| c) Gene amplification     | T (Ref. Robbin's patho) |
| d) Mosaicism              | F                       |
| e) Balanced translocation | T (and inversions)      |

**Mutation**

**Q. BRAF mutation is commonly seen in the following cancers:** (BSMMU-Residency - MD/MS, Paediatrics – March '19)

- a) follicular carcinoma of thyroid
- b) malignant melanoma
- c) adenocarcinoma of cervix
- d) small cell carcinoma of lung
- e) adenocarcinoma of colorectum

Ans. a) F b) T c) F d) F e) T

**Help Link:** BRAF mutation commonly occurs in : non-Hodgkin lymphoma(NHL), colorectal cancer, malignant melanoma, papillary thyroid carcinoma, non-small-cell lung carcinoma, adenocarcinoma of the lung, brain tumors including glioblastoma and pilocytic astrocytomas

(Ref. Robbins-9<sup>th</sup>, P-284+Wikipedia)

**Familial cancers**

**Q. Familial cancers are** (BSMMU – Non-Residency – MS, Basic science, Dentistry – July' 16)

- |                                    |   |
|------------------------------------|---|
| a) breast cancer                   | T |
| b) colorectal cancer               | T |
| c) medullary cancer of the thyroid | T |
| d) papillary cancer of the thyroid | F |
| e) stomach cancer                  | F |

**Q. Features that characterize familial cancers are (BSMMU – Residency – MD, MS, Basic Science – March' 15)**

- a) late age at onset
  - b) sometimes bilateral/multiple tumours
  - c) associated with specific marker phenotypes
  - d) tumours arise in two or more close relatives of the index case
  - e) siblings have 2-3 times greater risk than unrelated individuals
- Ans. a) F b) T c) F d) T e) T

**Q. Cancers with hereditary predisposition are (BSMMU – Residency - MD/MS, Basic science – March' 14)**

- |                                   |   |
|-----------------------------------|---|
| a) carcinoma of stomach           | F |
| b) bronchogenic carcinoma         | F |
| c) carcinoma of breast            | T |
| d) familial adenomatous polyposis | T |
| e) retinoblastoma                 | T |

**HELP LINK:**

#### Inherited cancer syndrome (Autosomal dominant)

Gene	Inherited predisposition
RB	Retinoblastoma
p53	Li-Fraumeni syndrome (various tumors)
p161 NK4A	Melanoma
APC	Familial adenomatous polyposis/ colon cancer
NF1, NF2	Neurofibromatosis 1 and 2
BRCA1, BRCA2	Breast and ovarian tumors
MEN1, RET	Multiple endocrine neoplasia 1 and 2
MSH2, MLH1, MSH6	Hereditary non-polyposis colon cancer
PATCH	Nevus basal cell carcinoma syndrome

#### Familial Cancers

Familial clustering of cases, but role of inherited predisposition not clear for each individual

Breast cancer

Ovarian cancer

Pancreatic cancer

#### Inherited autosomal recessive syndromes of defective DNA repair

- Xeroderma pigmentosum
- Ataxia-telangiectasia
- Bloom syndrome
- Fanconi anemia

**Q. Cancers that have hereditary predisposition are: (BSMMU - Basic Science; M. Phil, Diploma, July-'07)**

- |   |   |
|---|---|
| a) bronchogenic carcinoma               | F |
| b) gastric carcinoma                    | F |
| c) multiple endocrine neoplasia         | T |
| d) retinoblastoma                       | T |
| e) hereditary non polypoid colon cancer | T |

**Q. A hereditary predisposition to the development of tumors occur at the following sites: (BSMMU - M-Phil, Diploma, July-'06, MD-06Ja)**

- a) Retina
- b) Colon
- c) Uterus
- d) Skin
- e) Stomach

Ans.

- a) **True** (Between 6-10% of retinoblastomas are familial when the tumour is nearly always bilateral whereas in sporadic cases the tumour is more commonly unilateral. In the familial type, such patients are also at risk of developing osteosarcoma and soft tissue tumours. In the familial disease a mutant Rb gene is present, localized on chromosome Bq14, but in order to develop a tumour the intact copy of the gene must be lost in the retinoblasts through some form of somatic mutation.)
- b) **True** (The classic disorder of the colon which predisposes to the eventual development of malignancy in 100% of those affected is familial polyposis. This is transmitted in an autosomal dominant fashion. Typically the colon becomes carpeted at an early age by adenomata, the majority of which are of the tubular variety although some may have villous characteristics. The gene associated with FP has been mapped at chromosome 5q21.)
- c) **False** (There is no hereditary predisposition to endometrial cancer. The most significant factor in the development of endometrial cancer is prolonged oestrogen stimulation and endometrial hyperplasia. The importance of endometrial hyperplasia is borne out by the increased risk of endometrial cancer in females with oestrogen secreting tumours of the ovary, the increased risk in women receiving hormone replacement therapy and the decreased incidence of this disease in women castrated in early life or suffering from ovarian agenesis.)
- d) **True** (Both malignant melanoma and basal cell carcinomata have been shown in some cases to be due to an hereditary predisposition. In the case of MM genetic analysis has shown that the trait is inherited as an autosomal dominant, possibly involving a gene in the short arm of chromosome 1 near the Rh locus. In these cases the melanoma develops from a dysplastic naevus. In the case of inherited basal cell tumours, the tumours develop early in life and are commonly associated with abnormalities of bone, the nervous system, eyes and the reproductive organs.)
- e) **False** (Carcinoma of the stomach shows no hereditary predisposition. Although this tumour is more common in individuals with blood group A and there is an increased incidence in some racial groups e.g. the Japanese.)

**Q. Cancers that predisposition are have hereditary - (BSMMU - M-Phil, Diploma, July-'04)**

- |                                   |   |
|-----------------------------------|---|
| a) Familial adenomatous polyposis | T |
| b) Carcinoma of breast            | T |
| c) Bronchogenic carcinoma         | F |
| d) Carcinoma of stomach           | F |
| e) Retinoblastoma                 | T |

### Tumour suppressor gene

**Cancer suppressor gene/ Tumor suppressor gene/ Antioncogene:**

These genes are normal genes which switch off cell proliferation by acting on the cell cycle in G1. The physiologic function of these genes is to regulate cell growth, not to prevent tumor formation. Because the loss of these genes is a key event in many, possibly, human tumor and because their discovery resulted, the names tumor suppressor and antioncogene persist.

(Ref: Robbins+Cotran-9<sup>th</sup>, P-290)

**Selected Tumor Suppressor Genes Involved in Human Neoplasms**

Subcellular Locations	Gene	Function	Tumors Associated with Somatic Mutations	Tumors Associated with Inherited Mutations
Cell surface	TGF-β receptor	Growth inhibition	Carcinomas of colon	Unknown
	E-cadherin	Cell adhesion	Carcinoma of stomach	Familial gastric cancer
Inner aspect of plasma membrane	NF1	Inhibition of RAS signal transduction and of p21 cell cycle inhibitor	Neuroblastomas	Neurofibromatosis type 1 and sarcomas
Cytoskeleton	NF2	Cytoskeletal stability	Schwannomas and meningiomas	Neurofibromatosis type 2, acoustic schwannomas, and meningiomas
Cytosol	APC/β-catenin	Inhibition of signal transduction	Carcinomas of stomach, colon,	Familial adenomatous polyposis

Subcellular Locations	Gene	Function	Tumors Associated with Somatic Mutations	Tumors Associated with Inherited Mutations
Nucleus			pancreas; melanoma	coli/colon cancer
	PTEN	PI3 kinase signal transduction	Endometrial and prostate cancers	Cowden syndrome
	SMAD2 and SMAD4	TGF-β signal transduction	Colon, pancreas tumors	Unknown
Nucleus	RB1	Regulation of cell cycle	Retinoblastoma; osteosarcoma carcinomas of breast, colon, lung	Retinoblastomas, osteosarcoma
	p53	Cell cycle arrest and apoptosis in response to DNA damage	Most human cancers	Li-Fraumeni syndrome; multiple carcinomas and sarcomas
	WT1	Nuclear transcription	Wilms' tumor	Wilms' tumor
	P16/INK4a	Regulation of cell cycle by inhibition of cyclin-dependent kinases	Pancreatic, breast, and esophageal cancers	Malignant melanoma
	BRCA1 and BRCA2	DNA repair	Unknown	Carcinomas of female breast and ovary; carcinomas of male breast

(Ref: Robbins & Cotran-8<sup>th</sup>, P-287)**Question Bank****Q. Tumor suppressor genes (BSMMU – Residency – MD, MS, Basic Science – March’ 18)**

- a) suppress cancer cell proliferation
- b) are usually recessive in nature
- c) are also known as ‘anti oncogene’
- d) are responsible for 10% colonic cancers
- e) also function as gate keeper

Ans. a) T b) T c) T d) F e) T

**Q. Tumour suppressor genes are (BSMMU – Residency - MD, MS, Basic Science- March’ 17)**

- a) TP53
- b) RB gene
- c) K-RAS
- d) APC
- e) C-MYC

Ans. a) T b) T c) F d) T e) F

**Q. Cancer is a genetic disease because (BSMMU – Residency – MD, MS, Basic science, Dentistry – March’ 16)**

- a) all cancers show germ line mutation
- b) cells in a cancer are monoclonal
- c) polyploidy is a hallmark of in cancer cells
- d) somatic mutations occur in most cancers
- e) mutation of tumour suppressor genes cause cancer

Ans. a) F b) T c) F d) T e) T

**Q. Tumour suppressor genes associated with human cancer are - (BSMMU - M-Phil, Diploma, July-'04)**

- a) NF-1 in schwannoma
- b) Bcl-2 in pancreatic cancer
- c) C-mye in colonic carcinoma
- d) Rb in retinoblastoma
- e) BRACA-1 in breast carcinoma

Ans.

A. False (NF-1 associated with neuroblastomas &amp; NF-2 is associated with schwannomas and meningiomas)

**B. False****C. False** (C-myc is associated with Burkitt's lymphoma)**D. True** (Rb is associated with retinoblastoma and to a lesser extent osteosarcoma)**E. True** (BRCA-1 & BRCA-2 are associated with carcinoma of female & male breast & ovary)

Tumour suppressor gene	Familial syndrome	Sporadic cancers
APC	Colonic polyps and carcinoma	Carcinoma of stomach, colon, pancreas, melanoma
NF1	Neurofibromatosis type-1	Neurofibroma, juvenile myeloid leukaemia
NF2	Neurofibromatosis type-2(acoustic schwannoma, meningioma)	Schwannoma, meningioma
RB	Familial retinoblastoma syndrome (retinoblastoma, osteosarcoma, other sarcoma)	retinoblastoma, osteosarcoma, carcinoma breast colon, lung
VHL	Cerebellar hemangioblastoma, retinal angioma, RCC	RCC
TP53	Li-fraumeni syn.(diverse cancer)	Most human cancers
BRCA-1, BRCA-2	Familial breast and ovarian carcinoma,, carcinoma of male breast, CLL(BRCA-2)	Rare
WT-1	Familial Wilms tumour	Wilms tumour. Certain leukaemia
MEN-1	Pituitary, parathyroid, pancreatic endocrine carcinoma	Pituitary, parathyroid, pancreatic endocrine carcinoma

## Molecular basis of cancer

**Molecular basis of cancer:**

1. Nonlethal genetic damage lies at the heart of carcinogenesis.
2. A tumor is formed by the clonal expansion of a single precursor cell that has incurred genetic damage (i.e., tumors are clonal). (e.g., point mutations) or by chromosomal analyses (e.g., chromosomal translocations and copy number changes,
3. Four classes of normal regulatory genes—the growth-promoting proto-oncogenes, the growth-inhibiting tumor suppressor genes, genes that regulate programmed cell death (apoptosis), and genes involved in DNA repair—are the principal targets of cancer-causing mutations.
4. Carcinogenesis results from the accumulation of complementary mutations in a stepwise fashion over time
5. Mutations that contribute to the development of the malignant phenotype are referred to as *driver mutations*
6. Loss-of-function mutations in genes that maintain genomic integrity appear to be a common early step on the road to malignancy, particularly in solid tumors.
7. Mutations that lead to genomic instability not only increase the likelihood of acquiring driver mutations, but also greatly increase the frequency of mutations that have no phenotypic consequence, so-called *passenger mutations*, which are much more common than driver mutations

**Q. Cancers display following fundamental changes in cell physiology:** (BSMMU – Residency – MD, MS, Basic Science, Dentistry – March '18)

- a) sensitivity to growth-inhibitory signals
- b) self-sufficiency in growth signals
- c) evasion of necrosis
- d) immortality
- e) ability to evade host immune response

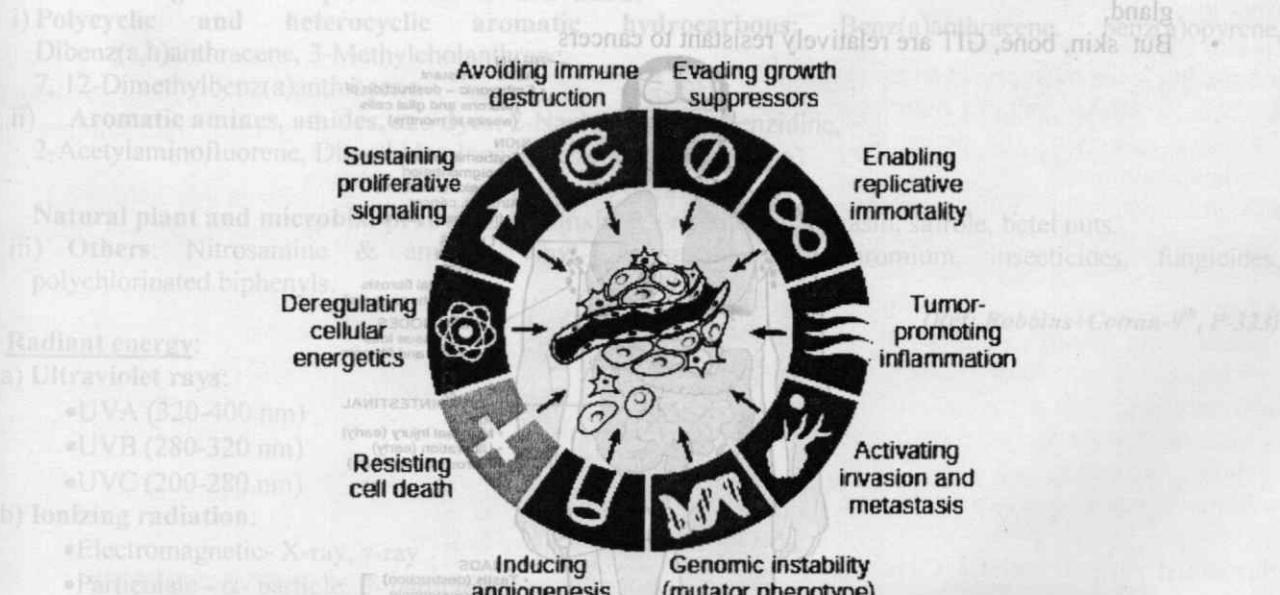
Ans. a) F b) T c) F d) T e) T

**Help link:****Cellular and Molecular Hallmarks of Cancer:**

All cancers display eight fundamental changes in cell physiology, which are considered the hallmarks of cancer. These changes consist of the following:

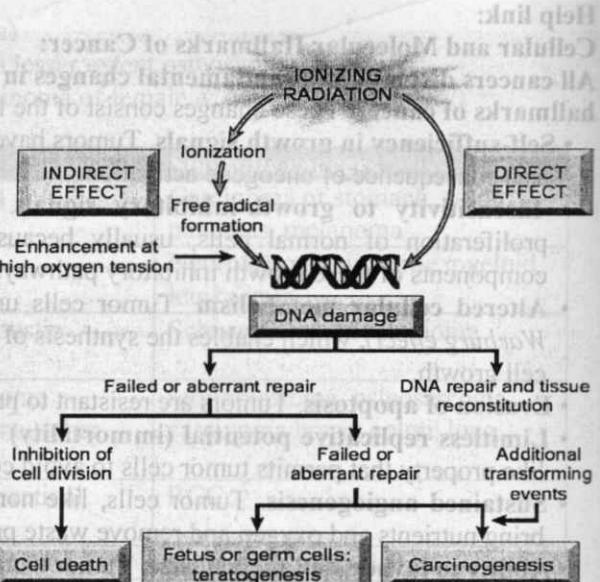
- **Self-sufficiency in growth signals.** Tumors have the capacity to proliferate without external stimuli, usually as a consequence of oncogene activation.
- **Insensitivity to growth-inhibitory signals.** Tumors may not respond to molecules that inhibit the proliferation of normal cells, usually because of inactivation of tumor suppressor genes that encode components of these growth inhibitory pathways.
- **Altered cellular metabolism.** Tumor cells undergo a metabolic switch to aerobic glycolysis (called the *Warburg effect*), which enables the synthesis of the macromolecules and organelles that are needed for rapid cell growth.
- **Evasion of apoptosis.** Tumors are resistant to programmed cell death.
- **Limitless replicative potential (immortality).** Tumors have unrestricted proliferative capacity, a stem cell-like property that permits tumor cells to avoid cellular senescence and mitotic catastrophe.
- **Sustained angiogenesis.** Tumor cells, like normal cells, are not able to grow without a vascular supply to bring nutrients and oxygen and remove waste products. Hence, tumors must induce angiogenesis.
- **Ability to invade and metastasize.** Tumor metastases are the cause of the vast majority of cancer deaths and arise from the interplay of processes that are intrinsic to tumor cells and signals that are initiated by the tissue environment.
- **Ability to evade the host immune response.** You will recall that the cells of the innate and adaptive immune system can recognize and eliminate cells displaying abnormal antigens (e.g., a mutated oncoprotein). Cancer cells exhibit a number of alterations that allow them to evade the host immune response.

## • Pro-carcinogens that require metabolic activation:

**Fig: Hallmarks of Cancer****How UV light causes cancer:**

- It is derived from sun
- Risk factors: fair skinned people, type of UV light, intensity of exposure, quantity of light absorbing melanin in skin.

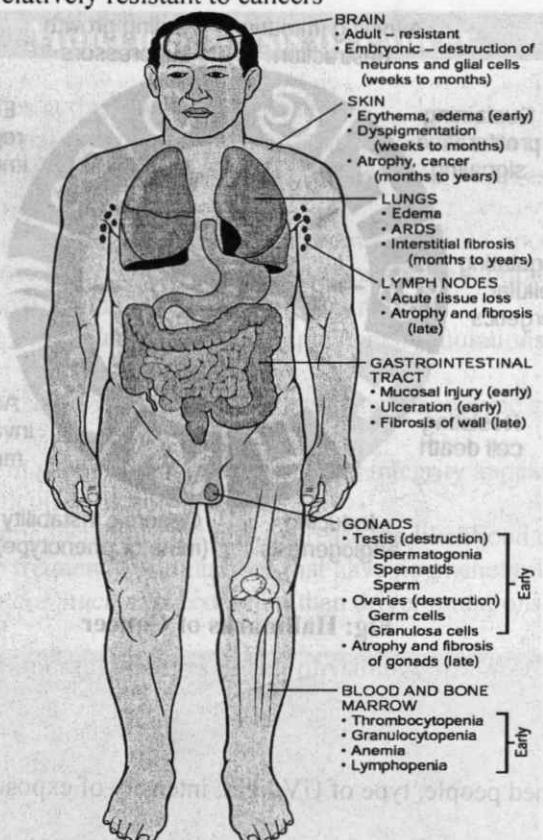
- Name of cancer: SCC, malignant melanoma, BCC
  - Non melanoma skin cancers are due to total exposure of UV light, melanoma skin cancers are due to intense intermittent exposure(sun bath)
  - Wavelength of UV light: UVA(320-400 nm), UVB(280-320 nm), UVC(200-280 nm).
  - UVB is responsible for cancers,
  - UVC is potent mutagenic, filtered by Ozone.
  - Mechanisms: formation of pyrimidine dimers in DNA, covalent cross linking, distorts DNA helix, fits to proper pairing,



**Figure 9-16** Effects of ionizing radiation on DNA and its consequences. The effects on DNA can be direct, or most importantly, indirect, through free radical formation.

### **Ionizing radiation:**

- Electromagnetic- X-ray, gamma rays
  - Particulate- alpha particle, beta particle, protons, neutrons
  - In Hiroshima and Nagasaki are- certain forms of leukaemia
  - Radiation induced cancers: myeloid leukaemias, thyroid cancers, carcinoma of breast, lung, salivary gland,
  - But skin, bone, GIT are relatively resistant to cancers



**Figure 9-18** Overview of the major morphologic consequences of radiation injury. Early changes occur in hours to weeks; late changes occur in months to years. ARDS, Acute respiratory distress syndrome.

## CARCINOGENS

**Q.** Following are procarcinogens (*BSMMU—Residency—MD/Basic science—March' 14*)

- |                     |   |
|---------------------|---|
| a) benzanthracene   | T |
| b) cycasin          | T |
| c) chlorambucil     | F |
| d) benzidine        | T |
| e) dimethyl sulfate | F |

**Help link:**

**Carcinogens:**

■ **Definition:** A large number of agents cause genetic damage and induce neoplastic transformation of cells. These are called **carcinogens**.

(Ref: Robbins+Cotran-9<sup>th</sup>, P-324)

■ **Classification:**

1. Chemical carcinogens
2. Radiant energy and
3. Oncogenic viruses and some other microbes.

(Ref: Robbins+Cotran-9<sup>th</sup>, P-324)

**1. Chemical carcinogen:**

• Direct-acting carcinogens:

- i) Alkylating agents:  $\beta$ -propriolactone, Dimethyl sulfate, Diepoxybutane, Anti-cancer drugs (cyclophosphamide, chlorambucil, nitrosoureas and others)
- ii) Acylating agents: 1-acetyl-imidazole, Dimethylcarbamyl chloride

• Pro-carcinogens that require metabolic activation:

- i) Polycyclic and heterocyclic aromatic hydrocarbons: Benz(a)anthracene, benz(a)opyrene, Dibenz(a,h)anthracene, 3-Methylcholanthrene, 7, 12-Dimethylbenz(a)anthracene.
- ii) Aromatic amines, amides, azo dyes: 2-Naphthylamine, benzidine, 2-Acetylaminofluorene, Dimethylaminoazobenzene (butter yellow)

**Natural plant and microbial products:** Aflatoxin B, griseofulvin, cycasin, safrole, betel nuts.

- iii) Others: Nitrosamine & amides, vinyl chloride, nickel, chromium, insecticides, fungicides, polychlorinated biphenyls.

(Ref: Robbins+Cotran-9<sup>th</sup>, P-323)

**B. Radiant energy:**

a) **Ultraviolet rays:**

- UVA (320-400 nm)
- UVB (280-320 nm)
- UVC (200-280 nm)

b) **Ionizing radiation:**

- Electromagnetic- X-ray,  $\gamma$ -ray
- Particulate -  $\alpha$ - particle,  $\beta$ - particle

(Ref: Robbins & Cotrans-9<sup>th</sup>, P-324)

**C. Oncogenic microbes:**

a) **Viruses:**

i. DNA oncogenic viruses:

- Human papillomavirus (1,2,4& 7)
- Epstein Barr virus
- Hepatitis B virus
- Kaposi sarcoma herpes virus

ii. RNA oncogenic virus: • Human T-cell leukaemia virus type-1

2. **Bacteria:** Helicobacter pylori

(Ref: Robbins & Cotrans-9<sup>th</sup>, P-325)

**Question Bank**

**Q. Polycyclic hydrocarbon may cause following cancers: (BSMMU – MD – January, 2010)**

- |            |   |
|------------|---|
| a) skin    | T |
| b) liver   | F |
| c) scrotum | F |
| d) lungs   | T |
| e) bone    | F |

**HELP LINK:****Polycyclic Aromatic Hydrocarbons:**

These agents represent some of the most potent carcinogens known. They require metabolic activation and can induce tumors in a wide variety of tissues and species. Painted on the skin, they cause skin cancers; injected subcutaneously, they induce sarcomas; introduced into a specific organ they cause cancers locally. The polycyclic hydrocarbons are of particular interest as carcinogens because they are produced in the combustion of tobacco, particularly with cigarette smoking, and are thought to contribute to the causation of lung and bladder cancers. Polycyclic aromatic hydrocarbons are also produced from animal fats in the process of broiling meats and are present in smoked meats and fish.

**Q. Which of the following lung cancer common in non-smokers: (BSMMU – MD – January, 2010)**

- |                         |   |
|-------------------------|---|
| a) small cell carcinoma | F |
| b) oat cell carcinoma   | F |
| c) adenocarcinoma       | T |
| d) alveolar carcinoma   | T |
| e) large cell carcinoma | F |

**Help link:****Health Effects of Tobacco**

- Smoking is the most prevalent preventable cause of human death.
- Tobacco smoke contains more than 2000 compounds. Among these are nicotine, which is responsible for tobacco addiction, and potent carcinogens—mainly, polycyclic aromatic hydrocarbons, nitrosamines, and aromatic amines.
- Approximately 90% of lung cancers occur in smokers. Smoking is also associated with an increased risk of cancers of the oral cavity, larynx, esophagus, stomach, bladder, and kidney, as well as some forms of leukemia. Cessation of smoking reduces the risk of lung cancer.
- Smokeless tobacco use is an important cause of oral cancers. Tobacco consumption interacts with alcohol in multiplying the risk of oral, laryngeal, and esophageal cancer and increases the risk of lung cancers from occupational exposures to asbestos, uranium, and other agents.
- Tobacco use is an important risk factor for development of atherosclerosis and myocardial infarction, peripheral vascular disease, and cerebrovascular disease. In the lungs, in addition to cancer, it predisposes to emphysema, chronic bronchitis, and chronic obstructive disease.
- Maternal smoking increases the risk of abortion, premature birth, and intrauterine growth retardation.

**Suspected Organ-Specific Carcinogens in Tobacco Smoke:**

Organ	Carcinogen
Lung, larynx	Polycyclic aromatic hydrocarbons 4-(Methylnitrosoamino)-1-(3-pyridyl)-1-buta-none (NNK) Polonium 210
Esophagus	N'-Nitrosonornicotine (NNN)
Pancreas	NNK
Bladder	4-Aminobiphenyl, 2-naphthylamine
Oral cavity (smoking)	Polycyclic aromatic hydrocarbons, NNK, NNN
Oral cavity (snuff)	NNK, NNN, polonium 210

(Ref: Robbins-9<sup>th</sup>, P-415)

**Q. The following malignancies are of infective origin (DMC – MD/ MS - January, 2010)**

- |                       |   |
|-----------------------|---|
| a. Burkitt's lymphoma | T |
| b. cervical carcinoma | T |
| c. thyroid carcinoma  | F |
| d. Kaposi's sarcoma   | T |
| e. ovarian carcinoma  | F |

**Help link:**

Malignancies	Oncogenic microbes
Burkitt's lymphoma	Epstein Barr virus
Cervical carcinoma	Human papilloma virus
Kaposi sarcoma	Kaposi sarcoma virus
Gastric carcinoma	<i>Helicobacter pylori</i>
Hepatocellular carcinoma	Hepatitis B virus
T cell leukaemia	Human T cell leukaemia virus type - 1

#### **Box: Cancer developments due to environmental factors**

- Both genetic and environmental factor can play role, but dominant role is environmental factors.
- Factors
  1. Infectious agents: 15 %, HPV
  2. Smoking: cancer in mouth, pharynx, larynx, esophagus, pancreas, UB, lung(90%).
  3. Alcohol: carcinoma of oropharynx(excluding lip), larynx, esophagus, alcoholic cirrhosis, HCC,
  4. Diet: colorectal carcinoma, prostate, breast carcinoma.
  5. Obesity: 14% cancer in men, 20 % in women.
  6. Reproductive history: exposure to estrogen increased cancers of breast and endometrium.
  7. Environmental carcinogens: UV rays, smog, arsenic, methotrexate, asbestos, grilled meat, high fat diet, alcohol.

## **Occupational cancer**

### **Occupational Cancers**

Agents or Groups of Agents	Human Cancer Site for Which Reasonable Evidence Is Available	Typical Use or Occurrence
Arsenic and arsenic compounds	Lung, skin, hemangiosarcoma	Byproduct of metal smelting; component of alloys, electrical and semiconductor devices, medications and herbicides, fungicides, and animal dips
Asbestos	Lung, mesothelioma; gastrointestinal tract (esophagus, stomach, large intestine)	Formerly used for many applications because of fire, heat, and friction resistance; still found in existing construction as well as fire-resistant textiles, friction materials (i.e., brake linings), underlayment and roofing papers, and floor tiles
Benzene	Leukemia, Hodgkin lymphoma	Principal component of light oil; despite known risk, many applications exist in printing and lithography, paint, rubber, dry cleaning, adhesives and coatings, and detergents; formerly widely used as solvent and fumigant
Beryllium and beryllium compounds	Lung	Missile fuel and space vehicles; hardener for lightweight metal alloys, particularly in aerospace applications and nuclear reactors

Agents or Groups of Agents	Human Cancer Site for Which Reasonable Evidence Is Available	Typical Use or Occurrence
Cadmium and cadmium compounds	Prostate	Uses include yellow pigments and phosphors; found in solders; used in batteries and as alloy and in metal platings and coatings
Chromium compounds	Lung	Component of metal alloys, paints, pigments, and preservatives
Nickel compounds	Nose, lung	Nickel plating; component of ferrous alloys, ceramics, and batteries; by-product of stainless-steel arc welding
Radon and its decay products	Lung	From decay of minerals containing uranium; potentially serious hazard in quarries and underground mines
Vinyl chloride	Angiosarcoma, liver	Refrigerant; monomer for vinyl polymers; adhesive for plastics; formerly inert aerosol propellant in pressurized containers

(Ref: Robbins & Cotran's-9<sup>th</sup>, P-278)**Question Bank****Q. Diseases arising from occupational exposure are (BSMMU – Residency – Dentistry – March' 18)**

- a) acrodermatitis enteropathica
- b) acute leukemia
- c) arsenicosis
- d) asbestosis
- e) aspergillosis

Ans. a) F b) T c) T d) T e) F

**Q. Inhalation of asbestos is associated with (BSMMU – Residency - MD, MS, Basic Science, Dentistry - March' 17)**

- |                       |                   |
|-----------------------|-------------------|
| a) sarcoidosis        | b) mesothelioma   |
| c) pulmonary fibrosis | d) lung carcinoma |
| e) leukaemia          |                   |

Ans. a) F b) T c) F d) T e) F

**Q. Occupations associated with high incidence of cancer includes (BSMMU – Residency – MD, MS, Basic science, Dentistry – March' 16)**

- |                     |                      |
|---------------------|----------------------|
| a) coal mining      | b) nickel workers    |
| c) asbestos workers | d) beryllium workers |
| e) tobacco industry |                      |

Ans.

a) **False** Although there is a high incidence of pneumoconiosis silicosis, tuberculosis and chronic bronchitis in coal miners, there is no evidence of an increased incidence of neoplasia directly related to this industry. Coal tar on the other hand contains potent carcinogens,

b) **True** A higher incidence of bronchial cancer and cancer of the nasal sinuses occurs in workers in contact with nickel or chrome. This is related to the inhalation of dust containing these materials.

c) **True** Workers who inhale asbestos have a higher than normal incidence of all types of cancer of the lung. The inhalation of blue asbestos is particularly associated with the development of mesotheliomas. Asbestos exists in two distinct geometric forms, the serpentine chrysotile which is composed of curly flexible fibres and the amphibole type composed of straight, stiff brittle fibres. The amphiboles include crocidolite and various other forms and this is the type which is particularly associated with the development of mesothelioma, although both types promote severe pulmonary interstitial fibrosis.

d) **True**

- e) False The preparation of tobacco and cigarettes does not hold any risk for industrial workers. The carcinogens in tobacco are coal tar products which form only when the tobacco is smoked. Nicotine is not carcinogenic.

**Q. Asbestosis is associated with (BSMMU – Residency – MD, MS, Basic – March' 15)**

- a) leukaemia
- b) mesothelioma
- c) oesophageal carcinoma
- d) colonic carcinoma
- e) angiosarcoma

Ans. a) F b) T c) T d) T e) F

**Q. Arsenic poisoning is related to (BSMMU – Non-Residency – MD, MS, Basic science, Dentistry – July' 15)**

- |                            |   |
|----------------------------|---|
| a) Bowen's disease         | T |
| b) malignant melanoma      | F |
| c) basal cell carcinoma    | F |
| d) keratoacanthoma         | F |
| e) squamous cell carcinoma | T |

**Q. Arsenic related tumours are (BSMMU – Residency - MD/MS, Basic science – March' 14)**

- |                               |   |
|-------------------------------|---|
| a) Bowen's disease            | T |
| b) melanoma                   | F |
| c) lymphangioma circumspectum | F |
| d) squamous cell carcinoma    | T |
| e) keratoacanthoma            | F |

**Q. Following chemicals responsible for corresponding occupational cancers: (BSMMU – MS - 10Ja)**

- a) asbestos, beryllium- lung cancer.
- b) arsenic- skin cancer
- c) chromium- prostate cancer
- d) benzene- hemangiosarcoma
- e) ethylene oxide- leukemia

**Q. Agents causing cancer in man include: (MD/MS (DMC)-02Ja)**

- a) Arsenic
- b) Asbestos
- c) Ionising radiation.
- d) Thorotrast.
- e) Ultra- violet light.

## Chronic inflammatory states and cancer

**Q. Chronic inflammatory conditions leading to malignant disease are (BSMMU – Non-Residency – MS, Basic science – July '18).**

- chronic osteomyelitis
- sarcoidosis
- asbestosis
- ulcerative colitis
- crohn's disease

Ans. a) T b) F c) T d) T e) T

**Q. Risk factors for malignancy are: (BSMMU – M. Phil. Diploma (Non-Residency)–March-2012, DMC & others – MD – March-2012)**

- |   |   |
|---|---|
| a) ulcerative colitis                       | T |
| b) gastric ulcer                            | F |
| c) atrophic gastritis in pernicious anaemia | T |
| d) haemangioma of the liver                 | F |
| e) familial adenomatous polyposis coli      | T |

**Help link:**

**Table 7-4 Chronic Inflammatory States and Cancer**

Pathologic Condition	Associated Neoplasm(s)	Etiologic Agent
Asbestosis, silicosis	Mesothelioma, lung carcinoma	Asbestos fibers, silica particles
Inflammatory bowel disease	Colorectal carcinoma	
Lichen sclerosis	Vulvar squamous cell carcinoma	
Pancreatitis	Pancreatic carcinoma	Alcoholism, germline mutations (e.g., in the trypsinogen gene)
Chronic cholecystitis	Gallbladder cancer	Bile acids, bacteria, gallbladder stones
Reflux esophagitis, Barrett esophagus	Esophageal carcinoma	Gastric acid
Sjögren syndrome, Hashimoto thyroiditis	MALT lymphoma	
Opisthorchis, cholangitis	Cholangiocarcinoma, colon carcinoma	Liver flukes ( <i>Opisthorchis viverrini</i> )
Gastritis/ulcers	Gastric adenocarcinoma, MALT lymphoma	<i>Helicobacter pylori</i>
Hepatitis	Hepatocellular carcinoma	Hepatitis B and/or C virus
Osteomyelitis	Carcinoma in draining sinuses	Bacterial infection
Chronic cervicitis	Cervical carcinoma	Human papillomavirus
Chronic cystitis	Bladder carcinoma	Schistosomiasis

(Ref: Robbins-9<sup>th</sup>, P-279)

## Grading & Staging of a tumour

**■ Grading:** Grading refers to the level of differentiation of the tumor.

**Grading of a tumour is based on:**

- The degree of differentiation of the tumour cells/ aggressiveness (degree of resemblance to normal counterpart, nuclear size, pleomorphism)
- The number of mitoses within the tumour as presumed correlates of the neoplasm's aggressiveness.

Grade I → > 75% cells are differentiated.

Grade II → 75 - 50% cells are differentiated.

Grade III → 50 - 25% cells are differentiated.

Grade IV → <25 % cells are differentiated.

**■ Staging:** Staging refers to the extent of spread of a cancer within the pt.

**Staging of a tumour is based on:**

- The size of the primary lesion,
- It's extent of spread to regional lymphnodes
- The presence or absence of blood bone metastasis

The major staging systems are -

1. UICC (Union Internationale Contre Cancer) employs TNM system.
2. AJC (American Joint Committee) employs different nomenclature

#### **TNM system:**

T for primary tumor →

- |     |                     |
|-----|---------------------|
| T0  | - carcinoma in situ |
| T 1 |                     |
| T 2 | - increasing size   |
| T 3 |                     |
| T 4 |                     |

N for regional lymph node involvement

- |    |                                      |
|----|--------------------------------------|
| N0 | - no nodal involvement               |
| N1 |                                      |
| N2 | - increasing number & range of nodes |
| N3 |                                      |

M for metastasis

- |    |                       |
|----|-----------------------|
| M0 | - no metastasis       |
| M1 | - metastasis present. |
| M2 |                       |

**AJC system:** This system divides all cancers into

- |           |  |
|-----------|--|
| Stage 0   |  |
| Stage I   | Considering the size of tumors,<br>nodal involvement & distant metastasis. |
| Stage II  |  |
| Stage III |  |
| Stage IV  |  |

**Importance of grading and staging:** selection of best form of therapy for the pt.

(Ref: Robbin's & Cotrans-9<sup>th</sup>, P-332)

#### **Question Bank**

**Q. Grading of a malignant tumor (BSMMU – Residency - MD/MS, Basic science, Paediatrics, Dentistry – March' 19)**

- a) depends on differentiation
- b) is also known as pathological staging
- c) is a light microscopic assessment
- d) is same for all organs
- e) correlates with tumor progression

Ans. a) T b) F c) T d) F e) F (Staging correlates with tumour progression)

**Q. Grading of a malignant tumor is based on (BSMMU – Diploma - Dentistry – July' 18)**

- a) nuclear pleomorphism
- b) size of the tumor
- c) number of mitosis
- d) regional lymph node involvement
- e) distant metastasis

Ans. a) T b) F c) T d) F e) F

**Q. Grading of a tumour is based on (BSMMU – Residency – Dentistry – March' 18)**

- a) degree of differentiation
- b) lymph node involvement
- c) number of mitosis
- d) site of tumour
- e) distant metastasis

Ans. a) T b) F c) T d) F e) F

**Q. Grading of cancer is based on (BSMMU – Non-Residency – MD, MS, Basic Science & Dentistry – July' 17)**

- a) number of mitoses
- b) spreading of cancer cells to regional lymph nodes
- c) size of primary tumor
- d) degree of differentiation of tumor cells
- e) presence of capsular invasion by tumor cells

Ans. a) T b) F c) F d) T e) F

**Q. Staging of a cancer (BSMMU – Residency – MD, MS, Basic science, Dentistry – March' 16)**

- a) is based on the size of the primary lesion
- b) is of greater clinical value than grading
- c) is based on the degree of differentiation of tumour cells
- d) depends on the presence or absence of blood borne metastasis
- e) is based on the number of mitoses within the tumour

Ans. a) T b) T c) F(Grading) d) T e) F (grading)

**Q. Grading of a malignant tumour is based on (BSMMU – Residency – MD, MS, Basic science, Dentistry – March' 16)**

- |                                   |   |
|-----------------------------------|---|
| a) cellular morphology            | T |
| b) regional lymph node metastasis | F |
| c) size of the tumour             | F |
| d) number of mitoses              | T |
| e) distant metastasis             | F |

**Q. Tumour staging involves (BSMMU – Non-Residency – MD, MS, Basic science, Dentistry – July' 15)**

- |                                    |   |
|------------------------------------|---|
| a) size of the tumour              | T |
| b) nuclear pleomorphism            | F |
| c) number of mitosis               | F |
| d) distant spread                  | T |
| e) regional lymph node involvement | T |

**Q. TNM staging of a malignant tumour (BSMMU – Residency - MD/MS, Basic science – March' 14)**

- a) is only a clinical assessment
- b) is an assessment of aggressiveness of the tumour
- c) can not be done after surgery
- d) takes account of the primary tumour size
- e) is important for treatment planning

Ans. a) F b) F c) F d) T e) T

**Q. Grading of a tumour is based upon (BSMMU – Non-Residency - MD/MS, Basic science – 13Ju)**

- a) size of the primary lesion
- b) extent of spread to regional lymph node
- c) degree of differentiation of tumour cells
- d) number of mitosis
- e) presence/absence of metastasis

Ans. a) F b) F c) T d) T e) F

**Q. The following grading/ staging are used in clinical oncology: (BSMMU – Residency – MD/MS – March' 13)**

- a) Ann-Arbor for lymphomas
- b) Gleason's for prostate carcinoma
- c) Duke for breast carcinoma
- d) Johnson for testicular tumours
- e) Broiler's for squamous cell carcinoma

Ans : a) T b) T c) F d) F e) F

**Help link:****Grading/ staging in oncology:**

- 1) **Breast Ca:** Nottingham/ Scarf-Bloor-Richardson system.
- 2) **Prostatic Ca:** Gleason's scoring system.
- 3) **Lymphoma:** Ann-Arbor staging system
- 4) **Colorectal Ca:** Duke's staging system
- 5) **Renal Ca:** Fuhrman staging system
- 6) **Bladder Ca:** Jewett staging system
- 7) **Melanoma:**
  - Breslow's classification (for thickness/ depth)
  - Clark's classification (for invasion)
- 8) **CLL:** Rai & Benet classification
- 9) **Multiple myeloma:** Durie-Salman staging system
- 10) **Ovarian/ Cervical Ca:** FIGO staging system

**Q. Malignant tumours are graded by:** (BSMMU – M. Phil, Diploma (Non-Residency)–March-2012, DMC & others – MD – March-2012)

- |                                       |   |
|---------------------------------------|---|
| a) observing cellular differentiation | T |
| b) presence of necrosis               | F |
| c) size of the tumour                 | F |
| d) TNM system                         | F |
| e) degree of anaplasia                | T |

**Q. Grading of a cancer is based on** (BSMMU – MD/MS (Residency) – January, 2011)

- |  |   |
|--|---|
| a) the degree of differentiation of tumour cells | T |
| b) the size of the primary lesion                | F |
| c) its extent of spread to regional lymph nodes  | F |
| d) number of mitosis within tumour               | T |
| e) presence or absence of blood borne metastasis | F |

**Q. Cancer staging is based on:** (BSMMU - M. Phil, Diploma – July '10)

- |                             |   |
|-----------------------------|---|
| a) cellular differentiation | F |
| b) extent of spread         | T |
| c) number of mitosis        | F |
| d) size of primary tumour   | T |
| e) metastasis               | T |

**Q. Staging of a malignant tumour:** (BSMMU – MS - January, 2010)

- |                                    |   |
|------------------------------------|---|
| a) is more important than grading  | T |
| b) is done by clinical assessment  | T |
| c) varies between different organs | T |
| d) can not be done for recurrence  | F |
| e) must include histological type  | F |

**Q. Grading of tumour:** (BSMMU - M. Phil, Diploma, July-09)

- |                                    |   |
|------------------------------------|---|
| a) Is same for all systems         | F |
| b) Depends on differentiation      | T |
| c) Is done by TNM system           | F |
| d) Require immunological technique | F |
| e) Roughly predicts prognosis      | T |

**Q. Grading of a malignant tumour:** (BSMMU - M-Phil, Diploma, July-'07)

- |   |   |
|---|---|
| a) is based on cellular differentiation       | T |
| b) is of greater clinical value than staging  | F |
| c) is done by microscopic examination         | T |
| d) requires immunohistochemistry              | F |
| e) usually correlates with its aggressiveness | T |

**Q. Grading of a tumour-** (BSMMU-MD/MS-07Ja)

- |  |   |
|--|---|
| a) Correlates with neoplasm's aggressiveness                 | T |
| b) Is based on the size of the lesion                        | F |
| c) Is based on the degree of differentiation of tumour cells | T |
| d) Refers to the presence/absence of blood borne metastasis  | F |
| e) Is based on the number of mitosis within the tumour       | T |

**Q. Grading of a tumour is based on-** (BSMMU-MD/MS-06Ja)

- |                                       |   |
|---------------------------------------|---|
| a) size of the primary lesion         | F |
| b) degree of differentiation          | T |
| c) presence of blood borne metastasis | F |
| d) spread to regional lymph nodes     | F |
| e) number of mitoses within tumour    | T |

**Q. Grading of tumour is based upon -** (BSMMU - M-Phil, Diploma, July-'05)

- |   |   |
|---|---|
| a) size of the primary lesion                 | F |
| b) extent of spread to regional lymph node    | F |
| c) degree of differentiation. of tumour cells | T |
| d) number of mitoses                          | T |
| e) presence/ absence of metastases            | F |

**Q. Grading of a tumor is based on-** (BSMMU – MD/MS - 05Ja)

- |                              |   |
|------------------------------|---|
| a) Degree of differentiation | T |
| b) Number of mitosis         | T |
| c) Lymph node involvement    | F |
| d) Size of the tumor         | F |
| e) Distant metastasis        | F |

**Q. Staging of cancers is based on -** (BSMMU - M-Phil, Diploma, July-'04)

- |   |   |
|---|---|
| a) Degree of differentiation                  | F |
| b) Size of primary tumour                     | T |
| c) Spread to regional lymph node              | T |
| d) Presence/absence of blood borne metastasis | T |
| e) Number of mitosis within tumour            | F |

**Q. Grading of a tumor-** (BSMMU-03Ju)

- |   |   |
|---|---|
| a) Depends on cellular differentiation    | T |
| b) Is a prognostic index                  | T |
| c) Is also called staging                 | F |
| d) Takes account of mitosis               | T |
| e) Is influenced by lymph node metastasis | F |

**Q. Factors associated with tumour grading are-** (BSMMU-MD/MS - 02Ja)

- |  |   |
|--|---|
| a) Number of lymphoid metastasis                           | F |
| b) Size of primary tumour                                  | F |
| c) Number of mitosis                                       | T |
| d) Degree of cytologic differentiation                     | T |
| e) Extent of tumour invasion in the surrounding structure. | F |

## Paraneoplastic Syndrome

### ■ Paraneoplastic syndromes:

Some cancer-bearing individuals develop signs and symptoms that cannot readily be explained by the anatomic distribution of the tumor or by the elaboration of hormones indigenous to the tissue from which the tumor arose; these are known as paraneoplastic syndromes. These occur in about 10% of persons with cancer.

#### **Importance:**

- They may be the earliest manifestation of an occult neoplasm.
- In affected patients they can cause significant clinical problems and may even be lethal.
- They may mimic metastatic disease and therefore confound treatment.

#### ■ Examples of paraneoplastic syndromes:

Clinical Syndromes	Major Forms of Underlying Cancer	Causal Mechanism
<b>ENDOCRINOPATHIES</b>		
Cushing syndrome	Small-cell carcinoma of lung Pancreatic carcinoma Neural tumors	ACTH or ACTH-like substance
Syndrome of inappropriate antidiuretic hormone secretion	Small-cell carcinoma of lung; intracranial neoplasms	Antidiuretic hormone or atrial natriuretic hormones
<b>Hypercalcemia</b>	Squamous cell carcinoma of lung Breast carcinoma Renal carcinoma Adult T-cell leukemia/lymphoma	Parathyroid hormone-related protein (PTHRP), TGF- $\alpha$ , TNF, IL-1
<b>Hypoglycemia</b>	Ovarian carcinoma Fibrosarcoma Other mesenchymal sarcomas	Insulin or insulin-like substance
<b>Polycythemia</b>	Renal carcinoma Cerebellar hemangioma Hepatocellular carcinoma	Erythropoietin
<b>NERVE AND MUSCLE SYNDROMES</b>		
Myasthenia	Bronchogenic carcinoma	Immunological
Disorders of the central and peripheral nervous system	Breast carcinoma	
<b>DERMATOLOGIC DISORDERS</b>		
Acanthosis nigricans	Gastric carcinoma Lung carcinoma Uterine carcinoma	Immunological; secretion of epidermal growth factor
Dermatomyositis	Bronchogenic, breast carcinoma	Immunological
<b>OSSEOUS, ARTICULAR, AND SOFT-TISSUE CHANGES</b>		
Hypertrophic osteoarthropathy and clubbing of the fingers	Bronchogenic carcinoma	Unknown
<b>VASCULAR AND HEMATOLOGIC CHANGES</b>		
Venous thrombosis (Trousseau phenomenon)	Pancreatic carcinoma Bronchogenic carcinoma Other cancers	Tumor products (mucins that activate clotting)
Nonbacterial thrombotic endocarditis	Advanced cancers	Hypercoagulability
Red cell aplasia	Thymic neoplasms	Unknown
<b>OTHERS</b>		
Nephrotic syndrome	Various cancers	Tumor antigens, immune complexes

(Ref: Robbins & Cotran's-9<sup>th</sup>, P-331)

**Question Bank**

**Q. Hypoglycaemia is associated with (BSMMU – Residency - MD, MS, Basic Science - March' 17)**

- a) fibrosarcoma
- b) pancreatic carcinoma
- c) renal cell carcinoma
- d) hepatocellular carcinoma
- e) papillary serous carcinoma

**Ans.** a) T b) F c) F d) T e) F

**Q. The paraneoplastic syndrome in renal cell carcinoma includes (BSMMU – Residency – MS, Basic science - March' 17)**

- a) polycythaemia
- b) leukaemoid reactions
- c) hypertension
- d) hypercalcaemia
- e) masculinization

**Ans.** a) T b) T c) T d) T e) T

(Ref: Khaleque Patho, P-170)

**Q. Hypercalcaemia occurs in (BSMMU – Residency – MS, Basic science - March' 17)**

- a) small cell carcinoma
- b) gastric carcinoma
- c) renal cell carcinoma
- d) breast carcinoma
- e) colonic carcinoma

**Ans.** a) F b) F c) T d) T e) F

(Ref: Davidson-22<sup>nd</sup>, P-271)

**Q. Paraneoplastic syndromes (BSMMU – Residency – MD, MS, Basic science, Dentistry – March' 16)**

- a) occur in about 90% of patient with malignant disease
- b) may represent the earliest manifestation of an occult neoplasm
- c) may even be lethal
- d) can mimic metastatic disease
- e) are relatively frequent in patients with cancer

**Ans.** a) F (10%) b) T c) T d) T e) F (infrequent)

**Q. Hypercalcemia as a paraneoplastic syndrome is observed in (BSMMU –Residency – MD – March' 15)**

- a) squamous cell carcinoma lung
- b) small cell carcinoma lung
- c) renal cell carcinoma
- d) breast cancer
- e) osteosarcoma

**Ans.** a) T b) F c) T d) T e) F

**Q. Hypercalcemia as a paraneoplastic syndrome is observed in (BSMMU –Residency – MS, Basic Science – March' 15)**

- a) squamous cell carcinoma lung
- b) small cell carcinoma lung
- c) renal cell carcinoma
- d) breast cancer
- e) hamartoma

**Ans.** a) T b) F c) T d) T e) F

**Q. Hypercalcaemia occurs in (BSMMU – Non-Residency – MD/MS, Basic science – July' 14)**

- a) breast carcinoma
- b) small cell carcinoma
- c) Paget disease
- d) hepatocellular carcinoma
- e) pancreatic carcinoma

**Ans.** a) T b) F c) T d) F e) F

**Q. Hypercalcaemia can be found in (BSMMU - Residency - MS - March' 14)**

- |                                 |   |
|---------------------------------|---|
| a) small cell carcinoma of lung | F |
| b) gastric carcinoma            | F |
| c) renal cell carcinoma         | T |
| d) breast carcinoma             | T |
| e) colonic carcinoma            | F |

**Q. The followings are examples of paraneoplastic syndrome: (BSMMU - M. Phil, Diploma, July-09)**

- |  |   |
|--|---|
| a) Cushing syndrome in lung carcinoma                        | T |
| b) Hypoglycemia in hepatocellular carcinoma                  | T |
| c) Hypercalcemia in breast carcinoma                         | T |
| d) Increased serum calcitonin medullary carcinoma of thyroid | F |
| e) Increased CA-125 level in ovarian cancer                  | F |

**Q. In renal cell carcinoma, the paraneoplastic syndrome includes— (BSMMU-MS-05Ja)**

- |                   |   |
|-------------------|---|
| a) Hypertension   | T |
| b) Hematuria      | F |
| c) Pain           | F |
| d) Hypercalcaemia | T |
| e) Erythrocytosis | T |

**HELP LINK:**

**■ The paraneoplastic syndromes in renal cell carcinoma:**

- Polycythaemia
- Hypertension
- Hypercalcaemia
- Cushing's syndrome
- Leukamoid reactions
- Masculinization
- Feminization

**Q. Hypercalcemia may be present in - (BSMMU - M-Phil, Diploma, July-'04)**

- |                                    |   |
|------------------------------------|---|
| a) Carcinoma of breast             | T |
| b) Carcinoma of pancreas           | F |
| c) Renal cell carcinoma            | T |
| d) Squamous cell carcinoma of lung | T |
| e) Small cell carcinoma of lung    | F |

**HELP LINK:**

**Hypercalcemia may be present in**

- |                                 |                                |
|---------------------------------|--------------------------------|
| Squamous cell carcinoma of lung | Breast carcinoma               |
| Renal carcinoma                 | Adult T-cell leukemia/lymphoma |

**Q. The following associations are true for paraneoplastic syndrome - (BSMMU-MS-01Ja)**

- |   |   |
|---|---|
| a) Myasthenia in breast cancer                      | F |
| b) Venous thrombosis in leiomyoma                   | F |
| c) Hypoglycemia in hepatocellular carcinoma         | T |
| d) Nephrotic syndrome in gastric adenoma            | F |
| e) Migratory thrombophlebitis in carcinoma pancreas | T |

**(Ref: Prof. Khaleque Sir)**

## Tumour Marker

■ **Definition:** Tumor markers are the biochemical indicators of the presence of a tumor.

### Selected Tumor Markers:

<b>HORMONES</b>	
Human chorionic gonadotropin	Trophoblastic tumors, nonseminomatous testicular tumors
Calcitonin	Medullary carcinoma of thyroid
Catecholamine and metabolites	Pheochromocytoma and related tumors
Ectopic hormones	See "Paraneoplastic Syndromes"
<b>ONCOFETAL ANTIGENS</b>	
$\alpha$ -Fetoprotein	Liver cell cancer, nonseminomatous germ cell tumors of testis
Carcinoembryonic antigen	Carcinomas of the colon, pancreas, lung, stomach, and heart
<b>ISOENZYMES</b>	
Prostatic acid phosphatase	Prostate cancer
Neuron-specific enolase	Small-cell cancer of lung, neuroblastoma
<b>SPECIFIC PROTEINS</b>	
Immunoglobulins	Multiple myeloma and other gammopathies
Prostate-specific antigen and prostate-specific membrane antigen	Prostate cancer
<b>MUCINS AND OTHER GLYCOPROTEINS</b>	
CA-125	Ovarian cancer
CA-19-9	Colon cancer, pancreatic cancer
CA-15-3	Breast cancer
<b>NEW MOLECULAR MARKERS</b>	
p53, APC, RAS mutants in stool and serum	Colon cancer
p53 and RAS mutants in stool and serum	Pancreatic cancer
p53 and RAS mutants in sputum and serum	Lung cancer
p53 mutants in urine	Bladder cancer

(Ref: Robbins & Cotran-9<sup>th</sup>, P-337)

### Question Bank

**Q.  $\alpha$ -fetoprotein is raised in (BSMMU – Residency – MS, Basic Science – March '18)**

- a) carcinoma of the colon
- b) hepatocellular carcinoma
- c) neuroblastoma
- d) yolk sac tumor of testis
- e) nephroblastoma

Ans. a) F b) T c) T d) T e) F

**Q. Serum  $\alpha$ -fetoprotein is raised in - (BSMMU – Non-Residency – MD, Basic – July '17)**

- a) cirrhosis of liver
- b) hepatocellular carcinoma
- c) hepatic hydatid cyst
- d) hepatic hemangioma
- e) gonadal teratoblastoma

Ans. a) T b) T c) F d) F e) T

**Q. Alpha fetoprotein is raised in (BSMMU – Non-Residency – MS, Basic Science – July' 17)**

- a) carcinoma of the colon
- b) hepatoblastoma
- c) neuroblastoma
- d) yolk sac tumor of testis
- e) nephroblastoma

**Ans.** a) F b) T c) F d) T e) F

**Q. Tumour markers are (BSMMU – Residency - MD, MS, Basic Science, Dentistry - March' 17)**

- a) TSH
- b) HbA1C
- c) PSA
- d) CEA
- e) CA-125

**Ans.** a) F b) F c) T d) T e) T

**Q. Carcinoembryonic antigen is raised in (BSMMU – Residency - Dentistry - March' 17)**

- a) colon cancer
- b) oral cancer
- c) prostatic cancer
- d) pancreatic cancer
- e) liver cancer

**Ans.** a) T b) F c) F d) T e) F

**Q. Tumour markers are (BSMMU – Residency – MD, MS, Basic science, Dentistry – March' 16)**

- |           |   |
|-----------|---|
| a) TSH    | F |
| b) Hb1Ac  | F |
| c) PSA    | T |
| d) CEA    | T |
| e) CA-125 | T |

**Q. Tumor markers are (BSMMU – Non-Residency – MD, MS, Basic science – July' 15)**

- |                                |   |
|--------------------------------|---|
| a) thyroid stimulating hormone | F |
| b) prostate specific antigen   | T |
| c) carcino embryonic antigen   | T |
| d) HbA <sub>1</sub> C          | F |
| e) $\alpha$ -feto protein      | T |

**Q. Tumour markers used for screening (BSMMU – Residency – MD, MS, Basic – March' 15)**

- a) calcitonin for medullary carcinoma of thyroid
- b)  $\alpha$ -fetoprotein for hepatocellular carcinoma
- c) neuron-specific enolase for small cell carcinoma
- d) CA-125 for breast cancer
- e) CA-19-9 for ovarian cancer

**Ans.** a) T b) T c) T d) F e) F

**Q. Alpha-fetoprotein is a tumor marker for (BSMMU – Residency - MS, Basic science – March' 14)**

- |                                    |   |
|------------------------------------|---|
| a) prostate cancer                 | F |
| b) hepatoma                        | T |
| c) Wilms' tumor                    | F |
| d) seminoma of testis              | F |
| e) gastro-intestinal stromal tumor | F |

**Q. Tumour markers are:** (BSMMU – Residency – MD/MS – March'13)

- a) Thyroid stimulating hormone (TSH)
- b) Prostate specific antigen (PSA)
- c) Carcinoembryonic antigen (CEA)
- d) HbA1C
- e)  $\alpha$  Feto protein

Ans : a) F b) T c) T d) F e) T

**Q. Tumor markers:** (BSMMU – Residency – MD/MS – March'13)

- a) Are one of the primary modality for the diagnosis of cancer
- b) Support in the diagnosis of the cancer
- c) Can determine the response of the cancer
- d) May indicate relapse during the following up period
- e) CA-125 is very much specific for ovarian carcinoma

Ans : a) F c) T d) T e) T

**Q. Tumour markers:** (BSMMU – M. Phil, Diploma (Non-Residency)–March-2012, DMC & others – MD/MS – March-2012)

- a) are biochemical indicators of tumours
- b) is only used to support the diagnosis
- c) have no role in follow up period of the disease
- d) are used for categorization of undifferentiated tumours
- e) can also be detected in stool and urine

Ans. a) T b) T c) F d) F e) T

**Q. The following tumor markers and malignancies are correctly paired:** (BSMMU – M. Phil, Diploma (Non-Residency)–March-2012, DMC & others – MS – March-2012)

- a) calcitonin— breast carcinoma
- b)  $\alpha$ -fetoprotein— hepatocellular carcinoma
- c) prostate specific antigen— carcinoma prostate
- d) carcino embryonic antigen — testicular teratoma
- e) human chorionic gonadotrophin — choriocarcinoma

Ans.a) F b) T c) T d) F e) T

**Q. Following serum tumour markers are useful for diagnosis of diseases mentioned -** (DMC-MD/ MS-10Ja)

- |  |   |
|--|---|
| a. human chorionic gonadotropin in testicular seminoma   | F |
| b. alpha fetoprotein in primary hepatocellular carcinoma | T |
| c. carcinoembryogenic antigen in carcinoma bronchus      | T |
| d. Ca-123 in breast carcinoma                            | F |
| e. calcitonin in medullary carcinoma thyroid             | T |

**Q. The facts about CA-125:** (BSMMU – MS - January, 2010)

- a) it is a mullerian differentiated antigen
- b) it found in high levels in germ cell tumours
- c) endometriosis is a cause of raised level
- d) is raised in atypical endometrial hyperplasia
- e) also raised in pancreatic tumours

Ans. a) T b) F c) T d) F e) F

#### HELP LINK:

CA 125 is a glycoprotein has been used for screening of epithelial cancers of the ovary. Value more than 35 U/ml suggestive of epithelial ovarian cancer. It is also used for monitoring a patient during chemotherapy and for follow up. But it is not a tumour specific antigen. There are several other conditions, where level of CA 125 is raised:

- Normal woman (1 percent)
- Carcinomas of the breast, lung and colon
- Endometriosis

- Pelvic inflammatory disease
- Peritonitis

**Q. Examples of tumour markers are:** (BSMMU - M. Phil, Diploma, July-'09)

- |                            |   |
|----------------------------|---|
| a) $\alpha$ -Feto protein  | T |
| b) CA 19—9                 | T |
| c) CA 125                  | T |
| d) Neuron specific enolase | T |
| e) Prostaglandins          | F |

**Q. Oncofetal antigens are:** (BSMMU - M. Phil, Diploma, July-09)

- |                               |   |
|-------------------------------|---|
| a) $\alpha$ - fetoprotein     | T |
| b) CA-125                     | F |
| c) Calcitonin                 | F |
| d) Carcinoembryonic antigen   | T |
| e) Prostatic acid phosphatase | F |

**Q. The clinically useful tumour markers are:** (BSMMU-MS - January, 2008)

- |                           |   |
|---------------------------|---|
| a) $\alpha$ - fetoprotein | T |
| b) PSA                    | T |
| c) Parathormone           | F |
| d) HCG                    | T |
| e) Noradrenaline          | F |

**Q. Tumor markers:** (BSMMU - M. Phil, Diploma, July-08)

- |   |   |
|---|---|
| a) are biochemical indicator for the presence of a tumor          | T |
| b) can be constructed as primary modality for diagnosis of cancer | F |
| c) are mainly used as a laboratory test to support the diagnosis  | T |
| d) are of value in determining response to therapy                | T |
| e) are all enzymes in nature                                      | F |

**Q. A rise in serum alpha feto protein is found in -** (MD/MS (DMC)-09Ja)

- |                                   |                                       |
|-----------------------------------|---------------------------------------|
| a. hepatocellular carcinoma       | T (90%)                               |
| b. gonadal teratoblastoma         | T (non-seminomatous germ cell tumour) |
| c. primary sclerosing cholangitis | F                                     |
| d. neural tube defect             | T                                     |
| e. haemochromatosis               | F                                     |

**Q. The following are the frequent causes of high serum alpha fetoprotein level:** (BSMMU – MD - 08Ja)

- |                                      |   |
|--------------------------------------|---|
| a) seminoma                          | F |
| b) metastatic carcinoma of the liver | T |
| c) hepatocellular carcinoma          | T |
| d) Cirrhosis of liver                | T |
| e) Oat-cell tumor of the lung        | F |

#### HELP LINK:

- $\alpha$ -fetoprotein is normally synthesized by the fetal liver. It may present in plasma in normal fetus.
- Alpha-feta protein can be elevated in all except dysgerminoma and choriocarcinoma.
- Elevated maternal  $\alpha$ -fetoprotein may indicate fetal neural tube defect, twin pregnancy, or fetal distress.
- Raised level can be found in case of hepatic carcinoma, germ cell tumours (not pure seminoma) and testicular teratoma
- It may be found in plasma in case of viral hepatitis, cirrhosis or liver metastasis.
- Raised amniotic fluid levels may be present in neural tube defects e.g. open spine bifida, anencephaly.
- Raised amniotic fluid level also may be found in congenital nephrotic syndrome, oesophageal and duodenal atresia)

(Ref: Davidson + Jaffcoat + Robbins Path)

**Q. The following tumour markers are oncofaetal antigens: (MD/MS (DMC)-08Ja)**

- |                        |   |
|------------------------|---|
| a. Human serum ACTH    | F |
| b. Alpha-fetoprotein   | T |
| c. Bence-Jones protein | F |
| d. HCG                 | F |
| e. CEA                 | T |

**Q. The following tumour markers are oncofaetal antigens: (BSMMU-06Ja)**

- |                        |   |
|------------------------|---|
| a. Human serum ACTH    | F |
| b. Alpha-fetoprotein   | T |
| c. Bence-Jones protein | F |
| d. HCG                 | F |
| e. CEA                 | T |

**Q. Serum tumour markers are: (MD/MS (DMC)-05Ja)**

- |             |   |
|-------------|---|
| a) Alpha FP | T |
| b) ALT      | F |
| c) PSA      | T |
| d) CK- MB   | F |
| e) CEA      | T |

**Q. Specific tumor markers of hepatoblastoma: (MD/MS (DMC)-04Ja)**

- |                              |   |
|------------------------------|---|
| a) gamma - GTP               | F |
| b) alpha fetoprotein         | T |
| c) Carcinoembryonic antigen  | F |
| d) Alpha-1 antitrypsin level | F |
| e) CA 19-9                   | F |

**Q. Specific tumor marker in hepatoblastoma - (M. phil, Diploma (DMC) – 03,July)**

- |                              |   |
|------------------------------|---|
| a) alpha fetoprotein         | T |
| b) carcinoembryonic antigen  | F |
| c) alpha-1 antitrypsin level | F |
| d) gamma-GTP                 | F |
| e) serum PSA                 | F |

**Q. Raised serum alpha-fetoprotein (AFP) levels are common in association with: (MD/MS (DMC)-02Ja)**

- |                             |   |
|-----------------------------|---|
| a) Carcinoma of the bladder | F |
| b) Carcinoma of the breast  | F |
| c) Hepatoma                 | T |
| d) Malignant lymphoma       | F |
| e) Malignant teratoma.      | T |

## Carcinoma In Situ

**Q. Carcinoma in situ (BSMMU –Residency – MD, MS, Basic Science, Dentistry – March '18)**

- a) is a premalignant condition
- b) usually reverts back to normal state
- c) can metastasize through lymphatics
- d) is common in cervix
- e) is to be diagnosed by biopsy

Ans. a) F b) F c) F d) T e) T

(Ref: Davidson + Jaffray + Ropper Part II)

**Q. The lesions that have histological features of squamous cell carcinoma in situ are:** (BSMMU-MD/MS-09Ja)

- a) Erythroplasia of Queyrat
- b) Bowenoid papulosis
- c) Erythroplakia
- d) Bowen's disease
- e) Leucoplakia

**HELP LINK:**

■ **Carcinoma in situ:** When dysplasia is marked & involve the entire thickness of epithelium, the lesion is known as carcinoma in situ.

It is a epithelial neoplasm which has all the cellular features of malignancy but has not yet invaded through the epithelial basement membrane. It is a pre-invasive stage of carcinoma. It may progress to invasive carcinoma. It is a very early stage and its excision causes complete cure of cancer.

■ **Examples:**

1. CIN (cervical intraepithelial neoplasm)
2. Carcinoma in situ in the epidermis of skin preceding the formation of invasive sq. cell carcinoma.
3. In situ cytological atypia in the lining epithelium of the respiratory tract in habitual smokers.
4. In situ ca of the female breast: a) Ductal ca in situ. b) Lobular ca in situ.
5. Dysplastic leukoplakia of mouth
6. Adenomas of colon
7. Bowen's disease of skin.
8. Actinic keratosis
9. Erythroplasia of Queyrat
10. Paget's disease of skin
11. Carcinoma in situ of the urinary bladder.
12. Bowenoid papulosis of penis

## Pre-Cancerous Conditions

**Box: Precursor lesions leads to cancer**

- Barret eosophagus
- Squamous metaplasia of bronchial epithelium due to smoking
- UB mucosa due to schistosoma infection.
- Pernicious anemia, chronic atrophic gastritis
- Non inflammatory hyperplasia can lead to cancer, eg: endometrial hyperplasia
- Leukoplakia
- Villous adenoma(leads to cancer in 50 % case)
- Rarely transform to cancer: pleomorphic adenoma, leiomyoma.
- Not at all: lipoma.
- T- cell deficient especially oncogenic viruses: increased risk of cancer.

**Precancerous disorders**

Organ	Diseases
Skin	<ul style="list-style-type: none"> <li>• Xeroderma pigmentosum</li> <li>• Solar actinic keratosis</li> <li>• Burn ulcer, varicose ulcer</li> <li>• Marjolin's ulcer</li> <li>• Dysplasia naevi</li> <li>• Leucoplakia</li> <li>• Radiodermatitis</li> <li>• Bowen's disease</li> </ul>

<b>Mouth</b>	<ul style="list-style-type: none"> <li>• Leukoplakia</li> <li>• Plummer Vinson/ Paterson-Kelly syndrome</li> </ul>
<b>Oesophagus</b>	Barrett oesophagus
<b>Stomach</b>	<ul style="list-style-type: none"> <li>• Chronic gastritis</li> <li>• Pernicious anaemia</li> <li>• Adenomatous polyp</li> <li>• Chronic gastric ulcer</li> </ul>
<b>Small intestine</b>	Crohn's disease
<b>Colon</b>	<ul style="list-style-type: none"> <li>• Familial adenomatous polyposis</li> <li>• Chronic ulcerative colitis</li> </ul>
<b>Hepato-biliary</b>	<ul style="list-style-type: none"> <li>• Cirrhosis of liver</li> <li>• Cholelithiasis</li> </ul>
<b>Lung</b>	Bronchial metaplasia & dysplasia
<b>Thyroid gland</b>	Autoimmune thyroiditis
<b>Bone</b>	Paget's disease
<b>Breast</b>	<ul style="list-style-type: none"> <li>• Intraductal epithelial hyperplasia</li> <li>• Small duct papilloma</li> <li>• Sclerosing adenosis</li> </ul>
<b>Female genital tract</b>	<ul style="list-style-type: none"> <li>• Cervical dysplasia</li> <li>• Endometrial hyperplasia</li> <li>• Dysplasia of vulva</li> <li>• Leucoplakia</li> </ul>
<b>Penis</b>	<ul style="list-style-type: none"> <li>• Leucoplakia</li> </ul>

(Ref: Robbins+Cotran-9<sup>th</sup>, P-279)

#### Question Bank

**Q.** Recognized precancerous conditions include (BSMMU – Residency – MS, Basic Science – March '18)

- a) Small intestinal polyps in Peutz-Jegher's syndrome
- b) colonic polyps of familial adenomatous polyposis coli
- c) xeroderma pigmentosum
- d) Bowen's disease
- e) molluscum sebaceum

Ans. a) F b) T c) T d) T e) F

**Q.** Precancerous conditions of the oral cavity are (BSMMU – Residency – MD, Basic Science, Dentistry – March '18)

- a) periodontitis
- b) erythroplakia
- c) leukoplakia
- d) aphous ulcer
- e) erythema multiforme

Ans. a) F b) T c) T d) F e) F

**Q.** Premalignant conditions for squamous cell carcinoma are - (BSMMU – Non-Residency – MD, MS, Basic Science & Dentistry – July' 17)

- a) solar keratosis
- b) Bowen's disease
- c) chronic eczema
- d) chronic ulceration
- e) keratoacanthoma

Ans. a) T b) T c) F d) F e) F

**Help link:****Skin premalignant condition:**

1. Solar actinic keratosis, burn ulcer,
2. varicose ulcer, leukoplakia, erythroplakia,
3. Dysplastic naevi, Marjolin ulcer,
4. Radio dermatitis, Bowens disease,
5. Erythroplasia of Quearet, Lichen planus

**Q. The followings are precancerous condition (BSMMU – Non-Residency – MS, Basic Science – July' 17)**

- a) cervical dysplasia
- b) villous adenoma of colon
- c) hypertrophic scar
- d) leukoplakia
- e) keloid

Ans. a) T b) T c) F d) T e) F

**Q. Precancerous conditions of skin are (BSMMU – Non-Residency – MS, Basic science, Dentistry – July' 16)**

- |                    |   |
|--------------------|---|
| a) Bowen's disease | T |
| b) blue naevus     | F |
| c) Paget's disease | F |
| d) papillary wart  | F |
| e) solar keratosis | T |

**Q. Precancerous lesions are (BSMMU – Residency – MD, MS, Basic science – March' 16)**

- a) villous adenoma of colon
- b) leukoplakia
- c) lichen planus
- d) atrophic gastritis
- e) peptic ulcer

Ans. a) T b) T c) T d) T e) F

**Q. Precancerous lesions are (BSMMU – Residency – MD, MS, Basic – March' 15)**

- a) erythroplakia
- b) atrophic gastritis
- c) microglandular hyperplasia of cervix
- d) atypical endometrial hyperplasia
- e) nodular hyperplasia of prostate

Ans. a) T b) T c) F d) T e) F

**Q. Precancerous lesions include (BSMMU – Non-Residency – MD/MS, Basic science – July' 14)**

- a) leukoplakia
- b) CIN III
- c) inflammatory nasal polyp
- d) Bowen disease of skin
- e) nodular goiter

Ans. a) T b) T c) F d) T e) F

**Q. The following conditions are pre-malignant (BSMMU – Non-Residency – MD, Basic science – July' 14)**

- a) Barrett's esophagus
- b) leukoplaka
- c) hot nodule of thyroid
- d) Paget's disease of bone
- e) aphthous ulcer of tongue

Ans. a) T b) T c) F d) T e) F

**Q. Followings conditions are precancerous (BSMMU – Non-Residency - MD/MS, Basic science – 13Ju)**

- |                                    |   |
|------------------------------------|---|
| a) leukoplakia of oral cavity      | T |
| b) nodular goitre of thyroid       | F |
| c) villous adenoma of colon        | T |
| d) squamous metaplasia in prostate | F |
| e) chronic ulcerative colitis      | T |

**Q. Examples of premalignant conditions are: (BSMMU – Residency – MD/MS – March '13)**

- a) Low grade squamous intraepithelial lesions (LSIL)
- b) CIN II
- c) Canker sores
- d) Crohn disease
- e) Erythoplakia

Ans : a) T b) T c) F d) T e) T

**Q. The following are premalignant conditions: (BSMMU – M. Phil, Diploma (Non-Residency)–March-2012, DMC & others – MS – March-2012)**

- |                                |   |
|--------------------------------|---|
| a) actinic keratosis           | T |
| b) Bowen's disease             | T |
| c) erythroplasia of De Queyrat | T |
| d) tylosis                     | F |
| e) giant hairy naevus          | F |

#### HELP LINK:

##### Skin precancerous disorders:

- Solar actinic keratoses of skin by sun exposure (face, dorsum of hands, arms, lips). Usually squamous cell carcinoma may develop.
- Persistent ulcers like burn ulcer, varicose ulcer. Squamous cell carcinoma may develop at the margin due to continuous epithelial hyperplasia. Such malignant ulcers are called Marjolin's ulcer.
- Dysplastic naevi are precursor of malignant melanoma
- Leucoplakia in perianal region
- Radiodermatitis

**Q. The following conditions may turn into malignancy (BSMMU – MS – Dentistry – March' 12)**

- a) Lichen planus
- b) Erythoplakia
- c) Villous adenoma
- d) Leukoplakia
- e) Fibrocystic disease of breast

Ans. a) T b) T c) T d) T e) T

**Q. The following conditions are considered precancerous: (BSMMU – M. Phil, Diploma (Non-Residency)–11Ju, DMC & others – MD/MS – 11Ju)**

- |                             |   |
|-----------------------------|---|
| a) Solar keratosis          | T |
| b) Chronic gastric ulcer    | T |
| c) Leukoplakia              | T |
| d) Psoriasis                | F |
| e) Villous adenoma of colon | T |

**Q. The following are precancerous lesions (BSMMU – MD/MS (Residency) – January, 2011)**

- |                             |   |
|-----------------------------|---|
| a) atrophic gastritis       | T |
| b) villous adenoma of colon | T |
| c) Peutz — Jegher's polyp   | T |
| d) leukoplakia              | T |
| e) bleeding peptic ulcer    | F |

**Q. The following conditions may turn into malignancy:** (BSMMU - MD - 11Ja)

- a) lichen scleroses et atrophicus
- b) lichen planus
- c) erythroplakia
- d) villous adenoma
- e) fibrocystic disease of the breast

Ans. a) T b) T c) T d) T e) T

**Q. The following conditions are precancerous -** (DMC – MD/ MS - January, 2010)

- |                         |   |
|-------------------------|---|
| a) tubular adenoma      | T |
| b) hamartomatous polyps | F |
| c) villous adenoma      | T |
| d) Metaplastic polyps   | F |
| e) lymphoid polyposis   | F |

**Q. Precancerous conditions include:** (BSMMU – MD - January, 2009)

- |                          |   |
|--------------------------|---|
| a) Molluscum contagiosum | F |
| b) Xeroderma pigmentosa  | T |
| c) Actinic keratosis     | T |
| d) Peutz-Jegher syndrome | T |
| e) Radiodermatitis       | T |

**Q. The followings are pre-cancerous conditions:** (BSMMU - M. Phil, Diploma, July-07)/

**Q. The following pathological conditions are regarded as pre-cancerous:** (DMC - M. Phil, Diploma, July-07)

- |                           |   |
|---------------------------|---|
| a) osteitis deformans     | T |
| b) leukoplakia            | T |
| c) fibroadenoma of breast | F |
| d) duodenal ulceration    | F |
| e) cervical erosion       | F |

**Q. An increased incidence of malignancy is seen in-** (BSMMÜ-07Ja)

- |                          |   |
|--------------------------|---|
| a) ulcerative colitis    | T |
| b) Scleroderma           | T |
| c) Diverticulosis        | F |
| d) Achalasia             | T |
| e) Hirschprung's disease | F |

**Q. Following are pre-malignant conditions:** (M. Phil, Diploma, July-07)

- |                                      |   |
|--------------------------------------|---|
| a) CIN-II                            | T |
| b) CIN-III                           | T |
| c) Yolk sac tumour                   | F |
| d) Ca-Cervix                         | F |
| e) Vulval intra-epithelial neoplasia | T |

**Q. Premalignant conditions are-** (BSMMU-Sur-04Ja)

- |                                 |   |
|---------------------------------|---|
| a) Keratoacanthoma              | F |
| b) Cystic hyperplasia of breast | T |
| e) Leukoplakia                  | T |
| d) Senile keratosis             | F |
| e) Intestinal polyposis coli    | T |

**Q. Pre-malignant condition of the skin are-** (DMC - MD/MS - 04Ja)

- |                          |   |
|--------------------------|---|
| a) eczematous dermatitis | F |
| b) lupus vulgaris        | F |
| c) solar keratosis       | T |
| d) melanoma              | F |
| e) marjolin's ulcer      | T |

**Q. The following are precancerous condition - (M. phil, Diploma (DMC) – 03,July)**

- |                                 |   |
|---------------------------------|---|
| a) erythroplakia of larynx      | T |
| b) sublingual varicosities      | F |
| c) multiple papilloma of larynx | F |
| d) herpetiform aphthous ulcers  | F |
| e) Bowen's disease.             | T |

**Q. The following are pre-malignant conditions- (BSMMU-MS-02Ja)**

- |                                |   |
|--------------------------------|---|
| a) Actinic keratoses           | T |
| b) Bowen's diseases            | T |
| c) Erythroplasia of De-Queyrat | T |
| d) Tylosis                     | F |
| e) Giant Hairy naevus          | T |

## Carcinoid syndrome

**Q. Clinical feature(s) of carcinoid syndrome include(s) (BSMMU – Residency - MD, Basic science – March' 19)**

- a) increased sweating
- b) vertigo
- c) flushing
- d) diarrhoea
- e) facial telangiectasia

Ans. a) F b) F c) T d) T e) F

**Help Link:**

**Carcinoid syndrome:**

- ✓ Paraneoplastic syndrome comprising the sign symptoms occurs secondary to carcinoid tumours.

**Pathogenesis:**

- ✓ Ileal tumours elaborate vasoactive substance P may cause carcinoid syndrome.

**Symptoms:**

- ✓ Flushing of face
- ✓ Diarrhoea
- ✓ Heart failure
- ✓ Bronchoconstriction

**Q. Carcinoid syndrome is associated with: (BSMMU – Residency – MD/MS – March'13)**

- a) Bronchial adenoma
- b) Pancreatic carcinoma
- c) Renal cell carcinoma
- d) Fibrosarcoma
- e) Gastric carcinoma

Ans : a) T b) T c) F d) F e) T

**Help link:**

**Carcinoid syndrome is associated with:**

- Bronchial adenoma
- Gastric carcinoma
- Pancreatic carcinoma

**Regarding carcinoid syndrome:**

- Carcinoid syndrome is due to carcinoid tumor.
- These tumors are commonly seen in the appendix, ileum and the rectum, though they may occur at any site in the GIT.
- Intestinal carcinoids are of low-grade malignancy. They metastasize to the liver and the lymph nodes.
- When secretions of the neoplastic enterochromaffin cells of the tumor with liver metastases are released, patient gets systemic symptoms of carcinoid syndrome.

- Serotonin (5-HT) is released and its metabolite (5-HIAA) is excreted in the urine. In addition to serotonin, other hormones are also released.
- The cardinal features of the syndrome are flushing and diarrhea (precipitated by exercise, alcohol or certain foods);
- Symptoms and signs due to local bowel tumors and liver metastases (hepatomegaly) may be present.
- Right-sided heart valve lesions may be present.
- Diagnosis is confirmed by 24-hour urinary 5-HIAA estimation.

### Radiosensitive tumours

Radiosensitivity	Name of cancers
<b>Highly radiosensitive</b>	Lymphoma, Leukaemia, seminoma, dysgerminoma
<b>Moderately radiosensitive</b>	SCC of skin, Head and neck tumors, Ca cervix, Ca lung, Ca oesophagus, Prostate, UB, Medulloblastoma, Ovarian cancer, Wilms tumor, neuroblastoma, Vaginal SCC
<b>Low radiosensitive</b>	Glioma(Astrocytoma, ependymoma, oligodendrogioma, Glioblastoma), Melanoma, osteosarcoma, RCC.

### Chemosensitive tumours

**Q. Chemosensitive cancers are (BSMMU – Non-Residency – MD, Basic science – July' 14)**

- testicular cancers
- melanoma
- lymphoma
- leiomyosarcoma
- rhabdomyosarcoma

Ans. a) T b) F c) T d) F e) T

Help link:

Name of tumour	Chemosensitive plus minus radiosensitive
Leukaemia	Chemosensitive plus minus radiosensitive
Lymphoma	Chemosensitive plus minus radiosensitive
Small cell lung carcinoma	Chemosensitive plus minus radiosensitive
Rhabdomyosarcoma, Wilms tumor	Chemosensitive plus minus radiosensitive
Advanced head and neck cancers	Chemosensitive plus minus radiosensitive
Oesophageal cancer	Chemosensitive plus minus radiosensitive
SCC of the anus	Chemosensitive plus minus radiosensitive
Advanced stage of cervical cancer and early laryngeal cancer	Radiosensitive

• **Usually responsible for chemotherapy**

- ALL
- CLL
- lymphoma:
  - Hodgkin's disease
  - intermediate and high grade non-Hodgkin's lymphoma, for example, diffuse large cell lymphoma, Burkitt's lymphoma, lymphoblastic lymphoma
- choriocarcinoma
- embryonal tumours
- myelomatosis
- oat cell carcinoma of bronchus

• **Often responsive tumours include:**

- breast carcinoma

- testicular teratoma
- ovarian carcinoma
- osteogenic sarcoma
- prostatic carcinoma
- AML
- CML

## Others

**Q. Spontaneous regression of cancer commonly occurs in (BSMMU – Non-Residency – Basic Science – July' 18)**

- a) breast cancer
- b) renal cell carcinoma
- c) malignant melanoma
- d) choriocarcinoma
- e) cancer of uterine cervix

Ans. a) F b) T c) T d) T e) F

**Help link:**

**Spontaneous regression of cancer commonly occurs:**

1. Testicular germ cell tumour, Neuroblastoma,
2. Malignant melanoma, Cutaneous BCC, Breast cancers,
3. Endometrial cancers, Thyroid cancers(Papillary, Follicular carcinoma),
4. Prostate, RCC, Leukaemia/Lymphoma).

**Q. Tumour surveillance cells of human body are (BSMMU – Residency - Dentistry - March' 17)**

- |               |                     |
|---------------|---------------------|
| a) macrophage | b) NK cell          |
| c) basophil   | d) cytotoxic T cell |
| e) B cell     |                     |

Ans. a) T b) T c) F d) T e) F

**Note:** Not B cells, but monoclonal antibody is responsible for tumour surveillance

**Q. Following tumors elaborate vinyl mandelic acid (VMA) in urine: (BSMMU – MD/MS – January, 2010)**

- |                         |   |
|-------------------------|---|
| a) Wilm's tumour        | F |
| b) Pheochromocytoma     | T |
| c) Medulloblastoma      | T |
| d) Neuroblastoma        | T |
| e) Ganglioneuroblastoma | F |

**HELP LINK:**

Excessive secretion of catecholamines can be confirmed by measuring the hormones (adrenaline/epinephrine, non-adrenaline/nor-epinephrine and dopamine) in plasma or their metabolites (e.g. Vanillyl-mandelic acid, VMA; conjugated metanephrine and non-metanephrine) in urine.

A high urinary level of vanillyl mandelic acid level can be found in:

- Tumours of sympathetic nervous tissue e.g. phaeochromocytoma, neuroblastoma.
- After MI, Major surgery
- Stressful conditions
- Drugs-Monoaminooxidase inhibitors, phenothiazines, methyldopa, tetracyclines, L-dopa, and beta blockers.
- Diet e.g. bananas, vanilla, tea, coffee, ice cream, chocolates.

- These tumors are commonly seen in the adrenals, heart and the rectum.
- Intestinal carcinoids are of low-grade malignancy. They metastasize to the liver.
- When secretions of the neuroectodermal chromaffin cells of the gut are released, patient gets systemic symptoms of carcinoid syndrome.

## Childhood Tumours

### Common Malignant Neoplasms of Infancy and Childhood:

0 to 4 Years	5 to 9 Years	10 to 14 Years
Leukemia	Leukemia	
Retinoblastoma	Retinoblastoma	
Neuroblastoma	Neuroblastoma	
Wilms tumor		
Hepatoblastoma	Hepatocellular carcinoma	Hepatocellular carcinoma
Soft-tissue sarcoma (especially rhabdomyosarcoma)	Soft-tissue sarcoma	Soft-tissue sarcoma
Teratomas		
Central nervous system tumors	Central nervous system tumors	Osteogenic sarcoma
	Ewing sarcoma	Thyroid carcinoma
	Lymphoma	Hodgkin disease

(Ref: Robin's & Cotran's-9<sup>th</sup>, P-475)

**Q. Embryonic tumours of infancy include (BSMMU – Non-Residency - MS – July' 19)**

- a) nephroblastoma
- b) osteosarcoma
- c) medulloblastoma
- d) cholangiocarcinoma
- e) lymphoepithelioma

Ans. a) T    b) T    c) F    d) F    e) F

**Q. Common childhood solid tumours are (BSMMU – Residency – MS, Basic Science – March' 18)**

- a) hemangioma
- b) nephroblastoma
- c) hepatoblastoma
- d) lymphangioma
- e) hamartoma

Ans. a) F    b) T    c) T    d) F    e) F

**Q. Potentially curable malignancy of childhood are (BSMMU – Residency - MD - March' 17)**

- a) Hodgkin's lymphoma
- b) acute lymphoblastic leukemia
- c) nasopharyngeal carcinoma
- d) nephroblastoma
- e) renal cell carcinoma

Ans. a) F    b) T    c) F    d) T    e) F

**Q. The embryonic tumours of infancy include (BSMMU – Non-Residency – MS, Basic science, Dentistry – July' 16)**

- a) cholangiocarcinoma
- b) hepatoblastoma
- c) lympho-epithelioma
- d) nephroblastoma
- e) osteosarcoma

F    T    F    T    F

**Q. Childhood malignant tumours are:** (BSMMU – M. Phil, Diploma (Non-Residency)–11Ju, DMC & others – MD/MS – 11Ju, (BSMMU – MD/MS (Residency) – 11Ja)

- |                   |   |
|-------------------|---|
| a) wilms tumour   | T |
| b) haemangioma    | F |
| c) neuroblastoma  | T |
| d) cystic hygroma | F |
| e) hepatoblastoma | T |

**Q. Common childhood tumors include -** (DMC – MD/ MS - January, 2010)

- |                             |   |
|-----------------------------|---|
| a. Wilm's tumor             | T |
| b. neuroblastoma            | T |
| c. seminoma                 | F |
| d. hepatocellular carcinoma | T |
| e. retinoblastoma           | T |

**Q. Childhood cancers are:** (BSMMU - M. Phil, Diploma, July-09)

- |                  |   |
|------------------|---|
| a) AML           | F |
| b) ALL           | T |
| c) Neuroblastoma | T |
| d) Wilm's tumour | T |
| e) Ca — stomach  | F |

#### **HELP LINK:**

#### **■ Malignant neoplasm of children:**

1. Acute leukaemia
2. Burkitt's lymphoma
3. Retinoblastoma
4. Teratoma
5. Wilm's tumor of kidney
6. Neuroblastoma
7. Glioma
8. Hepatoblastoma
9. Hepatocarcinoma
10. Soft tissue sarcoma (especially rhabdomyosarcoma)
11. CNS tumours
12. Ewing's sarcoma
13. Osteogenic sarcoma
14. Thyroid carcinoma
15. Hodgkin disease

**Sarcoma botryoides** or **botryoid sarcoma** or **botryoid rhabdomyosarcoma** is a subtype of embryonal rhabdomyosarcoma, that can be observed in the urinary bladder of infants and young children or the vagina in females, typically younger than age 8. The name comes from the gross appearance of "grape bunches" (*botryoid* in Greek).

#### **Clinical characteristics**

For botryoid rhabdomyosarcoma of the vagina, the most common clinical finding is vaginal bleeding<sup>[2]</sup> but vaginal bleeding is not specific for sarcoma botryoides: other vaginal cancers are possible. They may appear as a polypoid mass, somewhat yellow in color and are friable: thus, they (possibly) may break off, leading to vaginal bleeding or infections.

**Epidemiology:** Sarcoma botryoides normally is found in children under 8 years of age. Onset of symptoms occurs at age 3 years (38.3 months) on average.<sup>[3]</sup> Cases of older women with this condition have also been reported.<sup>[4]</sup>

**Angiosarcoma** is a malignant neoplasm of vessel walls. This may be in reference to blood or lymphatic vessels.

The term angiosarcoma is avoided in medical practice, as it does not define the tissue origin of the tumour precisely enough. Clinicians use more specific terms (for instance, Lymphangiosarcoma or Haemangiosarcoma) when describing tumours of vessel wall origin. The term is, however, used commonly in the United States and Canada when defining tumour type to patients and lay staff, as it has been felt the more specific terms descend too much into medical jargon.

Their location typically readily permits metastases to distant sites. Most tumours of visceral blood and lymphatic vessel walls are malignant. Neoplasia of superficial vessel tissues (for instance those in the vessels of the skin) usually carries a more favourable prognosis due to the reduced risk of malignancy, and the accessibility of the tumour site for treatment. However, haemangiosarcomas and lymphangiosarcomas of the skin are not uncommon

**Q. Tumours seen in childhood are:** (MD/MS (DMC)-08Ja)

- |                       |   |
|-----------------------|---|
| a) Sarcoma botyroides | T |
| b) Angiosarcoma       | F |
| c) Ewing's sarcoma.   | T |
| d) Brenner's tumour   | F |
| e) Wilm's tumor.      | T |

**Q. The embryonic tumours of infancy include:** (DMC - M. Phil, Diploma-07July)

- |                                      |
|--------------------------------------|
| a) nephroblastoma                    |
| b) osteogenic sarcoma (osteosarcoma) |
| c) medulloblastoma                   |
| d) cholangiocarcinoma                |
| e) lympho-epithelioma                |

Ans.

- a) **True** This renal neoplasm may appear as a rapidly growing tumour, 80% occurring under age four. Known also as a Wilm's tumour it accounts for approximately 8% of childhood malignancies. This tumour spreads rapidly by the blood stream producing metastases in the lungs. Microscopically it is composed of a mass of spindle-shaped cells in which acini and tubules are found.
- b) **False** Osteogenic sarcoma (osteosarcoma) arises from the cells of the primitive bone-forming mesenchyme. It is the commonest primary malignant tumour of bone excluding myeloma. Seventy-five per cent of sufferers are between 10 and 25 years of age but a similar tumour also occurs in older patients suffering from Paget's disease of bone.
- c) **True** These tumours develop in the cerebellum forming a soft greyishwhite mass which commonly protrudes into the fourth ventricle and spreads over the surface of the brain in a thin sheet to obscure the normal convoluted sirface. Microscopically they are composed of spherical or cylindrical cells which have little cytoplasm and no fibrils. Rosettes occur without a central cavity. These tumours are highly malignant but extremely radiosensitive.
- d) **False** These rare tumours develop from thec'ells of the biliary epithelium and are less common than true hepatocellular carcinoma. They are commonest in the Far East, in which the majority are associated with infestation by liver flukes.
- e) **False** An anaplastic squamous carcinoma heavily infiltrated with lymphocytes. This tumour is particularly common in adult Chinese in whom it is commonly associated wish a high titre of antibody to the Epstein—Barr virus.

(Ref: Smiddy)

**Q. Malignancies that commonly occur in children below 5 years of age include:** (PG-97Ja)

- |                      |   |
|----------------------|---|
| a) Leukemia          | T |
| b) Wilm's toumor     | T |
| c) Retinoblastoma.   | T |
| d) Osteosarcoma.     | F |
| e) Rhabdomyosarcoma. | T |

**Q. Embryonic tumors of infancy include:** (M. phil, Diploma (DMC) – 03Ju)

- |                        |   |
|------------------------|---|
| a) Nephroblastoma      | T |
| b) Osteosarcoma        | F |
| c) Medulloblastoma     | T |
| d) Cholangiocarcinoma  | F |
| e) Lympho-epithelioma. | F |

**Q. The embryonic tumor of infancy include:** (MD/MS (DMC)-01Ja)

- |                        |   |
|------------------------|---|
| a) Neuroblastoma.      | T |
| b) Osteogenic sarcoma. | F |
| c) Medulloblastoma.    | T |
| d) Cholangio-carcinoma | F |
| e) Nephroblastoma.     | T |

### Wilm's tumour (Nephroblastoma)

**Q. Wilm's tumour (Nephroblastoma)** (BSMMU –Residency - MD/MS, Basic science – March' 14)

- a) involves both the kidneys in about 5% of cases
- b) usually present as an abdominal mass
- c) rarely metastasizes to the lung
- d) has a 2 year survival rate of 90%
- e) usually affects adult

Ans. a) T b) T c) F d) F e) F

**Help link:**

**Wilm's tumor:** It is the most common primary renal tumor of childhood (2-5 years).

■ **Pathogenesis:**

- Wilm's tumor associated gene is located at chromosome 11p13.
- The risk of Wilm's tumor is increased in association with 3 congenital malformations:
  1. WAGR syndrome
  2. Denys-Drash syndrome
  3. Beckwith-Wiedemann syndrome.

■ **Morphology:**

**A. Gross:**

- A large, solitary, well-circumscribed mass.
- On cut section, the tumor is soft, homogenous and tan to gray.
- Occasionally foci of hemorrhage, cyst formation & necrosis.

**B. Microscopically:**

- Different stages of nephrogenesis.
- The classic triphasic combination of blastemal, stromal, and epithelial cell types is observed in the vast majority of lesions.
- Epithelial differentiation is usually in the form of abortive tubules or glomeruli.
- Stromal cells are usually fibrocytic or myxoid in nature, although skeletal muscle differentiation is not uncommon.
- Rarely, other heterologous elements are identified, including squamous or mucinous epithelium, smooth muscle, adipose tissue, cartilage, and osteoid and neurogenic tissue.
- Approximately 5% of tumors reveal **anaplasia**, defined as the presence of cells with large, hyperchromatic, pleomorphic nuclei and abnormal mitoses.

(Ref: Robbins & Cotran's-9<sup>th</sup>, P-479)

Angiosarcoma is a malignant neoplasm of vessel walls. This may be in reference to blood or lymphatic vessels.

## IMPORTANT MCQ OF TUMOURS

[Ref: Smiddy]

**Q. A tumour may be defined:**

- a) an abnormal mass of tissue
- b) a growth of tissue which exceeds and is uncoordinated with that of normal tissues
- c) a growth of tissue which is limited and coordinated with that of the rest of the body
- d) an abnormal increase in the cells of a tissue
- e) a malformation in which the various tissues of the part are present in improper proportionate distribution

Ans.

- a) **True** This is the opening phrase of the definition of a tumour as proposed by the late Professor R.A. Willis.
- b) **True** This is the second part of the definition of a tumour as constructed by Willis. It is followed by a third part, i.e. the growth of the tumour persists in the same excessive manner after cessation of the stimulus or stimuli which evoked the change.
- c) **False** A tissue, the growth of which is limited and coordinated with that of the rest of the body, is a malformation. A classic example is the cutaneous angioma, otherwise known as the 'port-wine stain' which grows only with the growth of the rest of the body and does not extend to involve a greater and greater territory of tissue.
- d) **False** This is the simple definition of hyperplasia. Hyperplasia usually occurs as:
  - (a) A compensatory response to loss of tissue of the same kind
  - (b) An increased functional demand which cannot be satisfied by the tissue already present
  - (c) Disturbed hormonal control of the activity of the tissue.
- e) **False** This is the definition of a hamartoma.

**Q. Broder's classification of tumours attempted to classify tumours according to:** (FCPS - Sur - 08Ju)

- a) their origin
- b) the degree of differentiation of a tumour
- c) the degree of stromal response
- d) the degree of lymphocytic infiltration of the tumour
- e) the number of mitoses found in a given area of the tumour

Ans.

- a) **False** Broder worked mainly with tumours of squamous epithelium.
- b) **True** This was the fundamental basis of Broder's classification. He recognised four grades of malignancy according to the degree of differentiation of the tumour. Grade 1, when more than 75% of the tumour cells were differentiated; Grade 4, when less than 25% of the tumour cells were differentiated with intermediate values in grades 2 and 3. This classification has been abandoned for many reasons:
  - (a) It is time consuming and, therefore, expensive
  - (b) Different parts of a tumour may show entirely different histological characteristics
  - (c) The results did not always correspond to the prognosis which is what Broder sought to establish. Thus a Grade I tumour of the skin has excellent prognosis whereas a Grade 1 bronchial carcinoma has a poor prognosis.
- c) **False** Stromal response, particularly of breast tumours, has been shown to influence prognosis but was not taken into account by Broder who was chiefly concerned with skin cancer.
- d) **False** Lymphocytic infiltration was not considered in Broder's classification although some importance is now attributed to this aspect. The degree of lymphocytic infiltration is regarded by many pathologists as an indication of the body's immunological response to the tumour.
- e) **True** The number of mitoses indicates a greater degree of malignancy. Various modifications of Broder's original classification have been proposed one of which, applied by Greenough to breast tumours, took into account three features of these glandular carcinomas:
  - (a) Tubule formation
  - (b) The regularity in size, shape and staining of the nuclei of the tumour cells
  - (c) Number of mitoses.

**Q. Neoplastic diseases may be associated with the following conditions: (BSMMU – MD - 05Ja)**

- a) Dermatomyositis
- b) Acanthosis nigricans
- c) Necrobiosis lipoidica
- d) Thrombophlebitis migrans
- e) Polyarteritis nodosa

Ans.

- A. True** Approximately 20% of patients suffering from dermatomyositis have an underlying malignant condition. Dermatomyositis is an inflammatory lesion of muscle in which a mononuclear infiltrate occurs between the muscle bundles which themselves show mild degree of degeneration and a loss of the normal transverse striations. The cutaneous lesions consist of erythematous patches with slight oedema. The classic rash takes the form of a lilac or heliotrope discolouration of the upper eyelids accompanied by periorbital oedema. Clinically, there is muscle weakness.
- B. True** Acanthosis nigricans is characterized by grey-black patches of verrucous hyperkeratosis. It is associated with visceral malignancy and occasionally with Hodgkin's disease or osteogenic sarcoma
- C. False** Necrobiosis lipoidica is not associated with neoplasia. It is a condition in which yellowish dermarcated lesions develop on the shins. Histologically the lesions may be necrobiotic and granulomatous. Diabetes is the underlying disease in approximately two third of affected individuals.
- D. True** Thrombophlebitis migrans is chiefly associated with tumours of the pancreas, lung, stomach and female genital tract. Clinically, repeated attacks of segmental thrombosis occurs in both the superficial and the deep veins, attacks which heal spontaneously.
- E. False** Polyartderitis nodosa is not associated with malignant disease but with hypersensitivity to a number of drugs including the sulphonamides and the anti- inflammatory agents such as phenylbutazone. It also occurs in HBV infections. The underlying cause is immune complex disease resulting in a necrotising arteritis affecting both deep and superficial vessels accompanied by polymorphonuclear leucocyte infiltration around the vessels.

**Q. General phenomena associated with neoplasia may include:**

- a) fever
- b) cachexia
- c) thrombotic episodes
- d) polycythaemia
- e) dermatomyositis

Ans.

- a) True** Fever, unassociated with infection, is particularly associated with the following tumours:  
 (a) Nephroblastoma  
 (b) Carcinoma of the renal tubules (hypernephroma)  
 (c) Lymphomata.  
 The cause of such pyrexia remains uncertain although it must be due to pyrogens formed by the breakdown products of the tumour.
- b) True** Cachexia is one of the common manifestations of widespread and terminal malignancy. The cause may be difficult to identify but in gastrointestinal tumours loss of appetite, bleeding and sepsis play a part.
- c) True** The classic thrombotic episode associated with neoplasia is that described by Trousseau in 1865, of recurrent superficial and deep venous thrombosis which undergo spontaneous remission; thrombophlebitis migrans. Rarely, a non-bacterial thrombotic endocarditis occurs in Widespread malignant disease and even rarer is disseminated intravascular coagulation.
- d) True** Polycythaemia does not normally complicate neoplasia, indeed the reverse is usually the case due either to blood loss, invasion of the red marrow or as yet unidentified causes. One exception is renal carcinoma which, by producing excessive erythropoietin, leads to a polycythaemia.
- e) True** Dermatomyositis is a disorder which affects the skin, muscles and blood vessels. A coagulative necrosis occurs together with a small round cell infiltration around the smaller arteries. Approximately 30% of all patients suffering from dermatomyositis between 50 and 70 years of age

are found to be suffering from disseminated malignant disease usually arising from the gastrointestinal tract and less frequently the bladder and bronchus.

**Q. The following tumours may secrete hormones: (FCPS - Sur - 09Ja)**

- a) carcinoid tumours
- b) choriocarcinoma
- c) benign teratoma of the ovary
- d) monodermal teratoma of the ovary
- e) seminoma

Ans.

- a) **True** Carcinoid tumours occur primarily in the gastrointestinal tract, most commonly in the ileum but they can in fact arise anywhere along the whole length of the gut and also in the bronchial tree, pancreas, biliary tree and ovary. The carcinoid syndrome, due to the secretion of 5HT (serotonin) arises in about 1% of all patients who develop a carcinoid whatever the primary site and in 20% of those in whom a gastrointestinal tumour develops associated with hepatic metastases. The importance of liver metastases is that serotonin is normally metabolized by the liver to an inactive end product 5-HIAA (5-hydroxyindole acetic acid). The release of 5HT causes intermittent flushing of the face, an increase in intestinal motility leading to diarrhoea and lesions on the pulmonary or tricuspid valves causing right sided heart failure.
- b) **True** Choriocarcinomas produce excessive quantities of chorionic gonadotrophin with the result that severe uterine bleeding occurs. Approximately 50% follow the development of a hydatidiform mole whilst 25% develop following perfectly normal pregnancies.
- c) **False** Benign teratoma of the ovary are usually cystic forming the so-called dermoid cyst of the ovary. They give rise to no hormonal secretions.
- d) **True** Monodermal or specialised teratomas are a rare group of ovarian tumours the most common of which are struma ovarii and carcinoid. Struma ovarii are composed of mature thyroid cells and may cause hyperthyroidism and carcinoid tumours of the ovary may, when large, give rise to the carcinoid syndrome.
- e) **True** The majority of seminomas of the testes do not secrete hormones but in approximately 10%, syncytial giant cells that resemble the syncytiotrophoblasts of the placenta are present. These cells secrete HGH (human gonadotrophic hormone) the serum level of which is raised.

**Q. Exfoliative cytology is useful for the diagnosis of: (FCPS - Sur - 09Ja)**

- a) meningioma
- b) bronchial cancer
- c) multiple myeloma
- d) cervical cancer
- e) vesical cancer

Ans.

- a) **False** The examination of cerebro-spinal fluid for exfoliated cells has not been shown to be particularly useful in the diagnosis of tumors of the CNS. Meningiomas do not generally shed cells into the CSF.
- b) **True** Malignant cells can be demonstrated in the sputum, bronchial washings and if present, in a pleural effusion, in patients suffering from bronchial cancer.
- c) **False** Although malignant plasma cells may be demonstrated occasionally in the peripheral blood in patients with multiple myeloma, this cannot strictly be called exfoliative cytology. Malignant cells in this condition are usually sought in marrow specimens.
- d) **True** Vaginal and cervical smears are commonly used to eliminate or confirm a diagnosis of carcinoma of the cervix or uterus. The abnormal cells which are pleomorphic and hyperchromatic are demonstrated by the use of a 'Papanicolaou' smear. This technique may also identify carcinoma in situ and various forms of dysplasia.
- e) **True** Exfoliative cytology is used extensively for the exclusion or diagnosis of tumors of the bladder. It is also extensively used in the screening of asymptomatic individuals working in the aniline dye industry.

**Q. The findings of the following substances in excessive quantities in the blood may be due to the presence of a specific type of tumour:**

- a) noradrenaline
- b) 5-hydroxytryptamine
- c) carcinoembryonic antigen
- d) prostaglandins
- e) calcium

**Ans.**

- a) **True** Excessive noradrenaline may indicate the presence of a phaeochromocytoma although this tumour also produces excessive quantities of adrenaline. The presenting symptoms of these tumours are determined by the relative concentration of the two hormones.
- b) **True** Excessive 5-hydroxytryptamine (serotonin) indicates the presence of a carcinoid tumour otherwise known as an argentaffinoma because the cytoplasm of the tumour cell can form deposits of silver from silver salts.
- c) **True** Carcinoembryonic antigen, one of the oncofetal antigens, is associated with gastrointestinal tumours. An estimation of this marker is of little initial assistance in their diagnosis but it is of some value as an indicator of metastatic recurrence since above normal values suggest that hepatic metastases have developed.
- d) **False** Although prostaglandins are found in a variety of tissues such as the seminal vesicles, lung, iris and renal medulla no tumour has been described in which this group of compounds is produced in excessive quantities.
- e) **True** Hypercalcaemia may indicate the presence of a benign or malignant parathyroid tumour or more commonly the presence of extensive osseous metastases. The latter arise most commonly from primary tumours of the breast, thyroid, bronchus, kidney or prostate.

**Q. Neuroblastomas are most common in:**

- a) children
- b) may differentiate into benign tumours
- c) the adrenal medulla
- d) the floor of the fourth ventricle
- e) sympathetic ganglia

**Ans.**

- a) **True** Neuroblastomas are one of the most common extracranial solid tumours of childhood accounting for some 20% of all deaths from malignant disease. In all, 90% occur below 5 years of age. The majority are sporadic but in about one quarter there is evidence of a hereditary disposition.
- b) **True** Although rare, neuroblastomas may differentiate into benign ganglioneuroma.
- c) **True** Almost one third of all neuroblastomas arise in the adrenal medulla. Arising in this site, they give rise to two distinct clinical syndromes, Pepper's syndrome associated with hepatomegaly and Hutchinson's syndrome associated with osseous metastases in the periorbital and orbital bones giving rise to periorbital bruising and possibly exophthalmos.
- d) **False** Rarely primary neuroblastomas do arise within the brain and are to be found in the cerebral hemispheres. The commonest intracranial tumour of nervous origin in childhood is the medulloblastoma which develops almost exclusively in the cerebellum. These latter tumours are highly malignant.
- e) **True** Neuroblastoma, otherwise known as sympatheticoblastoma may arise in the sympathetic ganglia. Regardless of the site of origin, there is a considerable degree of differentiation. Most are composed of small cells containing darkly staining nuclei and scant cytoplasm. A typical appearance is the arrangement of these cells in rosettes, the central spaces of which are filled with fibrillar extensions of the cells.

**Q. Hormone dependency may be exhibited by the following tumours:**

- a) malignant melanoma
- b) prostatic carcinoma
- c) follicular carcinoma of the thyroid
- d) bronchial carcinoma
- e) retinoblastoma

Ans.

**a) True** Although hormone therapy has no beneficial effect on malignant melanoma well documented reports do appear in the literature of such tumours regressing during pregnancy, presumably due to its hormonal effects.

**b) True** The scientific basis of hormone dependency was first established by Charles Huggins of Chicago after the Second World War when he discovered that carcinoma of the prostate was affected by altering its hormonal environment. Later he discovered that oophorectomy and adrenalectomy had a beneficial effect on disseminated breast cancer. It is interesting to note, however, that Beatson and others in the early part of this century had observed that the former operation sometimes produced great, although temporary, improvement in advanced breast cancer.

**c) True** The growth of both follicular and papillary tumours of the thyroid may be suppressed by the administration of thyroxine.

**d) False** Bronchial carcinomas are not hormone dependent although they occasionally produce hormones, in particular ACTH. When this occurs Cushingoid features develop.

**e) False** This is a tumour of infancy of which about 6% of cases are familial. There is no evidence of hormone dependency.

**Q. The commonest tumours of the central nervous system arise from:**

- a) the meninges
- b) primary tumours elsewhere in the body
- c) neuroglia
- d) the blood vessels
- e) nerve cells

Ans.

**a) False** Meningioma, developing from the arachnoid cells which lie in the deep surface of the dura, are only the third commonest tumour of the central nervous system.

**b) True** Secondary metastatic deposits are the commonest single group of tumours of the central nervous system. The tumours which most commonly metastasize to the central nervous system arise from the breast, bronchus, skin, melanoma and the gastrointestinal tract.

**c) True** Tumours of the neuroglia are known as glioma. The tumours of this group include astrocytomas, oligodendrogiomas and ependymomas. Approximately 80% of adult brain tumours are classified as fibrillary astrocytomas which, most commonly arise in the cerebral hemispheres in late middle age.

**d) False** True tumours of the blood vessels of the brain are rare. Haemangiomas form about 2% of cerebral tumours.

**e) False** Tumours of the central nervous system which arise from mature-looking neurons do occur but are rare. Usually such tumours are a mixture of both ganglion cells and glial cells forming tumors known as gangliogliomas. Pure gangliocytomas occur in the floor of the third ventricle, the hypothalamus and the temporal lobes. Their degree of malignancy is related to any glial content present in the tumour.

**Q. The 'doubling time' of a malignant tumour is affected by a number of factors including:**

- a) a decrease in cell cycle time
- b) exfoliation
- c) the percentage of cells in the resting phase
- d) the oxygen content of the tumour cells environment
- e) nuclear size

Ans.

- a) **False** The cell cycle time of tumour cells is unrelated to the growth of a tumour because although tumour cells pass through the same cell cycle as normal cells, i.e. G<sub>0</sub>, G<sub>1</sub>, S, G<sub>2</sub> and M, measurements suggest that the duration of these phases is for many tumours equal or longer than that of the normal cells from which the tumour is derived.
- b) **True** Exfoliation is a significant factor leading to the loss of tumour cells capable of division. This feature is particularly important in tumours of the gastrointestinal tract and urothelium.
- c) **True** The percentage of cells in the resting phase certainly determines the 'doubling time' of a tumour. The number of cells not in the resting phase, the growth fraction, appears to be high in the early phase of tumour growth, but as the tumour grows in size, cells leave the replicative pool in increasing numbers returning to the G<sub>0</sub> and G<sub>1</sub> phase. Different tumours have different growth fractions; thus some leukaemias and lymphomas have high fractions particularly when compared to more solid tumours. A further complication affecting the growth of a tumour is the heterogeneous nature of the cell population; thus some clones of tumour cells may only be capable of four or five divisions before dying.
- d) **True** Tumour cells in culture can form nodules between 1-2 mm in diameter before requiring a blood supply. However in solid tumours, necrosis occurs when the tumour extends more than 1-2 mm beyond a tumour blood vessel, indicating that beyond this limit the oxygen and nutritive requirements of the tumour cell cannot be sustained.
- e) **False** Nuclear size bears no relationship to the time taken for the division of malignant cells.

**Q. The interphase is:**

- a) situated between the prophase and metaphase
- b) a resting stage between cell division
- c) associated with growth of a cell
- d) accompanied by the accumulation of RNA
- e) situated between the anaphase and the telophase

Ans.

- a) **False** The prophase may be regarded as the beginning of cell division. During this phase the chromosomes become visible and during the metaphase the spindle is formed radiating from the centrioles situated at opposite poles of the cell.
- b) **True** During the interphase chromosomes cannot be detected within the nucleus as discrete structures by a light microscope.
- c) **True** The interphase is associated with the accumulation of ribonucleic acid in the cell.
- d) **True**
- e) **False** The interphase follows the telophase during which the chromosomes elongate and disappear as the new nuclear membrane forms and the spindle disappears.

**Q. The embryonic tumours of infancy include: (DMC - M. Phil, Diploma-07July)**

- a) nephroblastoma
- b) osteogenic sarcoma (osteosarcoma)
- c) medulloblastoma
- d) cholangiocarcinoma
- e) lympho-epithelioma

Ans.

- a) **True** This renal neoplasm may appear as a rapidly growing tumour, 80% occurring under age four. Known also as a Wilms' tumour it accounts for approximately 8% of childhood malignancies. This tumour spreads rapidly by the blood stream producing metastases in the lungs. Microscopically it is composed of a mass of spindle-shaped cells in which acini and tubules are found.
- b) **False** Osteogenic sarcoma (osteosarcoma) arises from the cells of the primitive bone-forming mesenchyme. It is the commonest primary malignant tumour of bone excluding myeloma. Seventy-five per cent of sufferers are between 10 and 25 years of age but a similar tumour also occurs in older patients suffering from Paget's disease of bone.

- c) **True** These tumours develop in the cerebellum forming a soft greyishwhite mass which commonly protrudes into the fourth ventricle and spreads over the surface of the brain in a thin sheet to obscure the normal convoluted surface. Microscopically they are composed of spherical or cylindrical cells which have little cytoplasm and no fibrils. Rosettes occur without a central cavity. These tumours are highly malignant but extremely radiosensitive.
- d) **False** These rare tumours develop from the cells of the biliary epithelium and are less common than true hepatocellular carcinoma. They are commonest in the Far East, in which the majority are associated with infestation by liver flukes.
- e) **False** An anaplastic squamous carcinoma heavily infiltrated with lymphocytes. This tumour is particularly common in adult Chinese in whom it is commonly associated with a high titre of antibody to the Epstein—Barr virus.

**Q. The following tumours may produce hormones: (FCPS - Sur - 09Ja)**

- a) choriocarcinoma
- b) bronchial carcinoma
- c) fibroma of the ovary
- d) islet cell tumours of the pancreas
- e) chromophobe pituitary adenoma

Ans.

- a) **True** Choriocarcinoma may be defined as a malignant tumour of trophoblastic origin. Most of these tumours are derived from gestational trophoblast and are a late complication of pregnancy. Non-gestational choriocarcinoma occasionally occurs, usually in the testes or in ovarian teratoma. Associated with pregnancy, approximately 50% arise in hydatidiform moles, 25% following abortions and 20% in a normal pregnancy. The tumours secrete chorionic gonadotrophin and in response to this stimulus ovarian cysts with luteinised theca interna are found in about one third of patients. The secretion of this hormone is an important feature, since failure of the level to fall to normal following treatment with chemotherapy indicates tumour is still present.
- b) **True** Bronchogenic carcinoma may secrete a variety of hormones producing thereby a number of paraneoplastic syndromes. The tumour like factors which may be secreted include:
- (1) An antidiuretic hormone inducing hyponatraemia
  - (2) Adrenocorticotrophic hormone causing Cushing's syndrome: this is the commonest hormonal manifestation
  - (3) Parathyroid related hormone causing hypercalcaemia
  - (4) Calcitonin causing hypocalcaemia
  - (5) Gonadotrophins causing gynaecomastia in the male
  - (6) Serotonin causing the carcinoid syndrome.
- c) **False** Benign fibromas of the ovary do not produce any hormonal disturbance but large tumours of this type may be associated with wasting, ascites and right sided hydrothorax, Meig's syndrome.
- d) **True** Islet cell tumours may be entirely non-functional, but if functional they may be associated with either hypoglycaemia due to the excessive and abnormal production of insulin or the Zollinger—Ellison syndrome due to the production of gastrin. This latter is associated with recalcitrant peptic ulceration.
- e) **True** Chromophobe adenomas constitute about one quarter of all pituitary tumours. Since they are most commonly non-functioning, they produce their effects chiefly by local pressure on adjacent structures, e.g. causing abnormal visual fields. Later, progressive panhypopituitarism develops causing hypothyroidism and hypogonadism. Although lacking clinical effects, immunochemical reactions reveal in some tumours demonstrable FSH and less frequently LH.

**Q. A hereditary predisposition to the development of tumors occur at the following sites: (BSMMU — MD - 06Ja)**

- A. Retina
- B. Colon
- C. Uterus
- D: Skin
- E. Stomach

Ans.

- A. True** Between 6-10% of retinoblastomas are familial when the tumour is nearly always bilateral whereas in sporadic cases the tumour is more commonly unilateral. In the familial type, such patients are also at risk of developing osteosarcoma and soft tissue tumours. In the familial disease a mutant Rb gene is present, localized on chromosome 11q14, but in order to develop a tumour the intact copy of the gene must be lost in the retinoblasts through some form of somatic mutation.
- B. True** The classic disorder of the colon which predisposes to the eventual development of malignancy in 100% of those affected is familial polyposis. This is transmitted in an autosomal dominant fashion. Typically the colon becomes carpeted at an early age by adenomata, the majority of which are of the tubular variety although some may have villous characteristics. The gene associated with FP has been mapped at chromosome 5q21.
- C. False** There is no hereditary predisposition to endometrial cancer. The most significant factor in the development of endometrial cancer is prolonged oestrogen stimulation and endometrial hyperplasia. The importance of endometrial hyperplasia is borne out by the increased risk of endometrial cancer in females with oestrogen secreting tumours of the ovary, the increased risk in women receiving hormone replacement therapy and the decreased incidence of this disease in women castrated in early life or suffering from ovarian agenesis.
- D. True** Both malignant melanoma and basal cell carcinomata have been shown in some cases to be due to an hereditary predisposition. In the case of MM genetic analysis has shown that the trait is inherited as an autosomal dominant, possibly involving a gene in the short arm of chromosome 1 near the Rh locus. In these cases the melanoma develops from a dysplastic naevus. In the case of inherited basal cell tumours, the tumours develop early in life and are commonly associated with abnormalities of bone, the nervous system, eyes and the reproductive organs.
- E. False** Carcinoma of the stomach shows no hereditary predisposition. Although this tumour is more common in individuals with blood group A and there is an increased incidence in some racial groups e.g. the Japanese.

**Q. Recognised precancerous conditions include:**

- the intestinal polyps of the small bowel occurring in the Peutz—Jegher syndrome
- the colonic polyps of familial polyposis (100%)
- xeroderma pigmentosum
- Bowen's disease
- molluscum sebaceum

Ans.

- a) False** The Peutz—Jegherz syndrome is a rare autosomal dominant condition in which multiple hamartomatous polyps develop throughout the gastrointestinal tract in association with hyperpigmentation around the lips, on the oral mucosa, genitalia and the palmar surface of the hands. Although the polyps themselves have no malignant potential, individuals suffering from this condition have an increased risk of developing carcinoma of the breast and lung.
- b) True** By definition familial polyposis is a condition in which a minimum of 100 polyps develop in the colon, although in the majority of cases many thousands may be present. The polyps appear in the second and third decades of life and within some 10—15 years become overtly malignant.
- c) True** Xeroderma pigmtonosa is a condition in which affected individuals are extremely photosensitive and in which there is an inherited inability to repair damage to DNA following exposure to ultraviolet light which causes the formation of pyrimidine dimers. The inability to repair these dimers results in an increased frequency of mutations leading to the early development of malignancy.
- d) True** Bowen's disease affects the genital regions in both males and females. Grossly the condition appears as a solitary grey-white plaque associated with ulceration. Histologically the epidermis show proliferation and numerous mitoses. The cells are markedly dysplastic but the dermal—epidermal boundary is sharply delineated by an intact basement membrane. In approximately 10—30% of sufferers however, over a period of many years the lesion becomes transformed into a typical squamous carcinoma.

**e) False** This tumour-like lesion occurs predominantly on the face and has a natural history of approximately six months. A nodule appears which grows rapidly for about eight weeks during which time the histological picture resembles that of a squamous carcinoma. After this the lesion stabilises and the exuberant epithelium which has formed slowly keratinises. This is then discharged and the lesion heals.

**Q. The following pathological conditions can be regarded as precancerous:**

- a) osteitis deformans
- b) leukoplakia
- c) fibroadenosis of the breast
- d) duodenal ulceration
- e) cervical erosions

Ans.

**a) True** Osteitis deformans also known as Paget's disease is a chronic bone dystrophy of unknown aetiology. Commonly it is polyostotic affecting the pelvis, spine and skull, but in about 15% of cases it is monostotic when it usually affects the tibia, ilium, femur or a single vertebral body. Histologically it is a disease marked by phases of bone resorption followed by bone formation. The net effect is an increase in bone mass which has a distorted architectural appearance. Although not considered a metabolic disorder, the serum alkaline phosphatase is raised and the urinary excretion of hydroxyproline is increased. Between 5—10% of patients affected by polyostotic disease develop osteosarcoma.

**b) True** Leukoplakia is a clinical term indicating the presence of white patches in a squamous epithelial mucous membrane. The condition affects the oral cavity and the vulva. In the mouth the condition is believed to be precipitated by chronic irritation. The whiteness of the affected epithelial surface is due to thickening of the epithelium and prolongation of the rete pegs. The papillae contain a chronic inflammatory infiltrate. As time passes the whiteness of the epithelium is converted to reddening due to loss of cell thickness and finally a carcinoma in situ develops leading eventually to invasive squamous carcinoma. The incidence of overt malignancy in leukoplakia is of the order of 5%, the onset of malignancy is clinically recognisable by the development of warty thickening within the plaques.

**c) False** Fibroadenosis of the breast, previously known as chronic mastitis and now as generalized cystic mastopathy, does not predispose to neoplastic change unless it is accompanied by marked epithelial hyperplasia. The latter is one of the four possible pathological changes seen in the breast, the others being fibrosis, cyst formation and adenosis. Adenosis indicates the formation of new breast lobules and/or the enlargement of pre-existing ones. The epithelial hyperplasia if referred to as epitheliosis, a term coined by Dawson to indicate hyperplasia of the ductal and acinar epithelium. It is only when this change is marked that the condition can be regarded as precancerous.

**d) False** Neoplastic changes do not appear to supervene in duodenal ulceration.

**e) False** The term cervical erosion is applied to the appearance of a red area around the external os spreading onto the exocervix. Histological examination shows that the normal opaque squamous epithelium has been replaced by transparent columnar epithelium. Should the replacement involve the cervical glands an appearance may be produced which is sometimes mistakenly interpreted as early invasive carcinomatous change.

**Q. The following are carcinogenic:**

- a) infra-red radiation
- b) ultra-violet radiation
- c) house dust
- d) soot
- e) moulds

Ans.

**a) False** Long wave infra-red irradiation is not associated with tumour development.

- b) **True** The ultraviolet portion of the solar spectrum is divisible into wave lengths. Of these, the middle band with a wave length of 280—320 nm is believed to be the cause of skin cancers and melanomata. The carcinogenic effect is believed to be due to the formation of pyrimidine dimers in DNA which, when unrepaired, lead to larger transcriptional errors and in some cases malignancy. The degree of risk from UVR not only depends on its wavelength but also on the intensity of exposure and the quantity of light absorbing melanin in the skin. Thus UVR is a more potent carcinogen in fair skinned people.
- c) **False** There are no carcinogens in normal house dust. This should be compared to some industrial occupations, e.g. workers in asbestos factories, in which dust may play an important role in the development of malignant disease. A condition associated with house dust is allergy, causing hay fever and bronchial asthma, chiefly due to antigens from the house dust mite, *Dermatophagoides pteronyssinus*.
- d) **True** Soot is a carcinogenic agent because of its contained coal tar products including 3,4 benzpyrene. Cancer of the scrotum occurring in chimney sweeps was the first occupational cancer to be described by Percival Pott in 1775.
- e) **True** Aflatoxin is a carcinogen produced by *Aspergillus flavus*, a species of *Aspergillus* found on the surface of peanuts. It is believed to be a major cause of hepatocellular cancer in the black population of Africa

**Q. The following chemicals are indirect-acting carcinogens, i.e. require metabolic conversion to become carcinogenic:**

- 1, 2, 5, 6 dibenzanthrazine
- cyclophosphamide
- $\beta$ -naphthytamine
- acetyl salicylic acid
- 4-dimethylamino-azobenzene

Ans.

- a) **False** Applied to the skin of mice this chemical acts to initiate cellular changes by causing permanent damage to the cellular DNA. When stimulated by a wide range of non-specific substances such as phenol, turpentine or croton oil in the area previously treated by an initiator a malignant, tumour develops, the latter substances acting as promoters (or co-carcinogens). In the absence of a promoter carcinogenesis does not occur.
- b) **False** Cyclophosphamide is a weak direct acting carcinogen like other alkylating agents in this group. Because the alkylating agents exert their therapeutic effects as anticancer agents by damaging cellular DNA, it is this same action which renders them direct carcinogenic agents.
- c) **True** In the past  $\beta$ -naphthylamine was responsible for the high incidence of bladder cancer in workers in the aniline dye and rubber industries. After absorption it is hydroxylated into an active carcinogen and then detoxified by conjugation with glucuronic acid. When excreted in the urine, the non-carcinogenic conjugate is split by the urinary enzyme gluronidase to release the active electrophilic reactant which is carcinogenic.
- d) **False** Aspirin is a potent cause of gastric erosions and thus gastric bleeding but so far no association has been found between it and tumour formation.
- e) **True** 4-dimethylamino-azobenzene or butter yellow has been used for colouring foodstuffs. Fed to rats and mice it is a potent inducer of hepatic cancers.

**Q. The following infections are associated with the development of cancer:**

- clostridial infections
- HBV infection
- EBV infection
- chlamydial infections
- schistosomiasis

Ans.

- a) False** Clostridia are Gram-positive anaerobic spore bearing organisms and are not known to have any neoplastic association. *Clostridium welchii*, *oedematiens* and *histolyticum* cause gas gangrene with *Cl. welchii* also causing severe food poisoning. *Clostridium tetani* causes tetanus and *Clostridium botulinus*, botulism, a severe and often fatal toxæmic disease resulting from the ingestion of contaminated food.
- b) True** Hepatitis B virus infection, the cause of 'serum hepatitis' is associated in two ways with hepatocellular carcinoma of the liver:
- (1) an acute infection may be followed by a persistent infection which may progress to chronic hepatitis followed by cirrhosis. In about 10% of patients so affected a hepatocellular carcinoma develops.
  - (2) in areas of the world in which the prevalence of HBV infection is high as in some parts of Africa, e.g. Mozambique, a high incidence of hepatocellular carcinoma occurs. In these cases the HBV infection begins in infancy following a vertical transmission from the mother, this results in a carrier state in which there is a 200 fold increased risk of developing HCC in early adult life, not necessarily associated with pre-existing cirrhosis.
- c) True** The Epstein-Barr virus, a member of the herpes family, has been implicated in four different types of human tumour, Burkitt's lymphoma, B-cell lymphoma in immunosuppressed individuals, particularly if they have been infected with the human immunosuppressed deficiency virus, some cases of Hodgkin's disease and nasopharyngeal carcinomas. EBV infects the epithelium of the nasopharynx and B lymphocytes. Burkitt's lymphoma is a neoplasm of B lymphocytes and is the most common childhood tumour in Central Africa and New Guinea.
- d) False** The chlamydia are not associated with neoplastic disease. They are infectious agents about 300 nm in diameter which cause trachoma, ophthalmia neonatorum, lymphogranuloma venereum and psittacosis. They cannot be cultured or normal culture media and have to be grown in eggs or tissue culture.
- e) True** The deposition of schistosome eggs in the wall of the bladder causes metaplasia of the bladder mucosa to occur from the normal transitional cell to a squamous cell epithelium. The great majority of bladder tumours developing in schistosomiasis are of squamous type, only about 30% being transitional cell carcinoma.

#### **Q. An Increase in the frequency of malignant disease occurs in the following conditions:**

- a) following the long term administration of immunosuppressive agents
- b) large bowel Crohn's disease
- c) coeliac disease
- d) ulcerative colitis
- e) xeroderma pigmentosum

**Ans.**

- a) True** Following homotransplantation, long term immunosuppressive therapy is required. In such patients continued suppression of the immune system leads to the development of lymphomas, most commonly immunoblastic B-cell lymphomas. Other types of tumour are rarely encountered.
- b) False** Malignant disease does not appear to follow long term granulomatous disease of the large bowel.
- c) True** In coeliac disease, otherwise known as gluten sensitive enteropathy, there is a long term risk of T-cell lymphomas developing in the small bowel. The fundamental disorder is a sensitivity to gluten which contains the protein component of wheat known as gliadin. Large numbers of B cells sensitised to gliadin appear in the small bowel mucosa and biopsy shows marked atrophy and blunting of the villi, but increased mitotic activity in the crypts.
- d) True** Chronic ulcerative colitis followed by an increase in large bowel malignancy. All recorded series show that the incidence of malignancy in this disease increases with the length of the clinical history and the severity of the disease.
- e) True** Xeroderma pigmentosum is a classical premalignant condition. Sufferers from this inherited disease rapidly develop skin cancer after exposure to ultra violet light.

**Q. An enhancement of tumour growth or an increased Incidence of tumour formation may occur:**

- a) following the long term administration of immunosuppressive drugs
- b) following immunological enhancement
- c) due to the release of soluble antigens by the tumour cells
- d) due to an alteration of T-cell function
- e) due to the excessive production or release of lysosomal enzymes

Ans.

- a) True** An increase in the incidence of non-Hodgkin's lymphoma has been reported in patients undergoing long term immunosuppressive treatment with drugs such as azathioprine. This drug is commonly used following renal transplantation or for the treatment of autoimmune diseases such as systemic lupus erythematosus.
- b) True** Immunological enhancement of tumour growth develops because of the production of 'blocking' antibody. This protects the tumour antigens from any cell-mediated immune response which the presence of the tumour provokes. In an experimental animal immunological enhancement of a transplantable tumour can be provoked by the prior immunization of the recipient with a dead tumour extract before the injection of live tumour cells.
- c) True** Tumours may shed soluble tumour specific transplantation antigens (tSTA) into the circulation which then react, with the antigen reactive sites on effector T cells thus reducing the severity of the cell-mediated immune response mounted to effect destruction of the tumour. This is one of the causes of a tumour 'sneaking through' a powerful immune response.
- d) True** T lymphocytes may exert a suppressor as well as an effector action in the body's immune response mounted against a tumour. The suppressor T lymphocytes form a distinct sub-population differing from the effector cells and distinguished by their different surface (Ly) antigens. A balance between suppressor and effector lymphocytes forms the regulatory basis of the immune response.
- e) False** Lysosomal enzymes; chiefly found in the macrophages, are important in degrading antigen prior to its presentation to the lymphocytes. These enzymes are mainly hydrolytic and proteolytic and thus are effective, following the activation of the macrophages by lymphokine, in destroying tumour cells, and microorganisms which have undergone phagocytosis.

**Q. The following are specific markers for certain specific types of malignancy:**

- a) 5-HIAA
- b)  $\alpha$ -fetoprotein
- c) Bence—Jones protein
- d) chorionic gonadotrophin
- e) carcinoembryonic antigen

Ans.

- a) True** 5-HIAA is a specific marker for carcinoid tumours of the gastrointestinal tract, 5-hydroxyindoleacetic acid is the inactive metabolite of 5-hydroxytryptamine. Increased levels occur in the blood in patients suffering from carcinoid tumours of the gastrointestinal tract because 5HT, if secreted by the tumour, is degraded in the liver.
- b) False**  $\alpha$ -fetoprotein is a glycoprotein normally synthesized in early fetal life by the yolk sac, fetal liver and gastrointestinal tract. Abnormal levels are particularly found in adult life in some 60—70% of patients suffering from hepatocellular carcinoma of the liver, embryonal carcinomas and yolk sac tumours of the testes. However, the presence of this substance is not conclusive evidence of malignancy since elevated levels may occur in cirrhosis, massive liver necrosis and fetal neural abnormalities.
- c) True** Bence—Jones proteins are free light chains of the immunoglobulin molecules that are present in the urine in patients suffering from multiple myeloma. They have  $\alpha$  or  $\lambda$  antigenic determinants. These proteins precipitate on heating the urine to 80°C but return into solution at higher temperatures.
- d) True** Large amounts of chorionic gonadotrophin are produced in normal pregnancy and following the development of hydatidiform moles or choriocarcinoma. In the latter, therefore, urine pregnancy tests are strongly positive.
- e) False** CEA is normally produced in the embryonic tissue of the gut, pancreas and the liver. It is a complex glycoprotein elaborated by many different neoplasms. Thus it is present in some 60-90% of patients

suffering from carcinoma of the colon, 50—80% suffering from pancreatic neoplasms and 50% suffering from gastric or mammary cancer. It may also rise in non-neoplastic conditions such as Crohn's disease and ulcerative colitis and hepatitis. However in colonic carcinoma, the level correlates with the tumour load and an elevated level following treatment is indicative of residual disease.

**Q. The incidence of tumour is increased in:**

- a) sarcoidosis
- b) Wiskott—Aldrich syndrome
- c) ataxia telangiectasis
- d) patients treated over long periods with corticosteroids
- e) patients receiving azathioprine

Ans.

- a) **False** Despite the depression of certain parameters of T-lymphocyte function which occurs in sarcoidosis there is no evidence of any increase in the incidence of malignancy in this disease.
- b) **True** The Wiskott—Aldrich syndrome is a sex linked recessive disease which causes the affected children to suffer from atopic eczema, thrombocytopenia and an increased susceptibility to infection. Although the thymus is morphologically normal, there is a progressive secondary depletion of T lymphocytes in the peripheral blood and the paracortical areas of the lymph nodes. The serum contains increased amounts of IgA and IgE, normal of IgG but decreased amounts of IgM. Eventually failure of T-lymphocyte function is followed by an increased incidence of lymphomas.
- c) **True** Ataxia telangiectasis is an autosomal recessive condition in which the thymus is hypoplastic. Delayed hypersensitivity reactions are depressed and plasma concentrations of IgA and IgG fail. A considerable number of patients develop malignant lymphomas or lymphatic leukaemia. The disease usually presents in infancy with cerebellar ataxia due to the associated atrophy of the cerebellar cortex and demyelination of the cerebellar peduncles.
- d) **False** There is no evidence that prolonged treatment with corticosteroids predisposes to tumour development.
- e) **True** In any patient receiving immunosuppressive drugs over long periods there is an increased incidence of lymphomas.

## Fixatives & Laboratory techniques

### Fixatives

#### **FIXATION:**

It is the process by which the cellular constituents are fixed in a chemical and physical state so that they can withstand subsequent treatment with various reagent with minimum loss, distortion or decomposition.

It involves killing of the cells rapidly and inhibiting the enzymatic destruction i.e. autolysis. Macrotubules are stabilized and aggregated. Proteins are denatured and some active group e.g.  $\text{NH}_4^+$  of protein and  $\text{PO}_4$  of nucleic acid are exposed. Cell membrane are altered. Before fixation gross examination is done to note down colour, quantity and appearance of the specimens. Fixation done with 10% formaline for overnight at room temp.

Volume of formaline used = 10 times of the tissue.

#### **Fixatives:**

- Chemical substance which are used to preserve / stabilize biological material prior to microscopy or other examination.
- Purpose:
  - Keep the tissue as like as life as possible after resection or death.
  - To preserve the microanatomy
  - To prevent autolysis and putrefaction
  - To prevent change of the volume & shape
  - To minimize any loss of molecule from the specimen.

#### **Classification:**

##### **1) Aldehydes:**

- Formaldehyde,
- Glutaraldehyde(for electron microscope),
- Acetone

##### **2) Oxidizing agents:**

- Osmium tetroxide,
- Potassium permanganate
- Potassium dichromate

##### **3) Protein denaturing agents:**

- Methyl alcohol, Ethyl alcohol.

##### **4) Physical agents:**

- Microwave(45- 55 degree)

##### **5) Others:** mercuric chloride, picric acid,

#### **Commonly used Fixatives: (Cytofixatives)**

- 95% ethanol
- 95% rectified spirit
- 80% isopropanol
- Absolute methanol
- Ether : 95% ethanol (1:1)
- Carnoy's fixative/ Absolute alcohol
- Spray fixatives (hair spray)

#### **10% Formaline:**

- 10% formalin (10%buffered formalin/ 10% neutral formalin)
- 40 % formaldehyde power mixed with 900 ml distilled water.
- Minimum shrinkage

- Cheap and easily available
- Irritant to eyes, nose and throat
- Does not fix carbohydrate
- Produce a brown pigment

**Advantage of using 10% formaline (contains 4% formaldehyde):**

- i. Tissue can be preserved for prolonged period.
- ii. It prevents growth of bacteria.
- iii. It is compatible with most of the common stains.

**Other fixatives are:**

- Zenker's fixative
- Bouin's fluid
- Absolute alcohol
- Carnoy's fixative
- Universal fixative

**Function of preservatives:**

- Stabilize the tissue.
- Prevent post-mortem changes.
- Hardens the tissue which facilitate sectioning.
- Promote affinity of tissue towards certain dyes.

**Other preservative are:** Mercuric chloride, absolute alcohol.

**Carnoy's fixatives:**

- Composed of –
  - Absolute alcohol - 60 ml
  - Chloroform - 30 ml
  - Glacial acetic acid- 10 ml
- Advantage:
  - rapid fixative for urgent sample,
  - excellent nuclear fixative,
  - preserve glycogen
- Disadvantage:
  - severe shrinkage of tissue
  - Soft tissue preservation not good

**Bouin's fixatives**

- Used in bone marrow trephine biopsy sample
- Composed of
  - picric acid
  - formaldehyde
  - glacial acetic acid
- Colour is yellow
- Other use: testicular biopsy fixation.

**Zenker's Fixatives**

- Composed of
  - Mercuric chloride
  - Potassium permanganate
  - Glacial acetic acid
  - Distilled water
- Used in kidney, LN, testis
- Best fixative for light microscope

**Main factors for fixation:**

- Hydrogen ion conc.(PH)
- Temperature
- Penetration
- Osmolality
- Concentration
- duration

**Question Bank**

**Q. Functional purpose of fixatives in biopsy samples includes** (BSMMU – Non-Residency – MD, MS, Basic Science & Dentistry – July' 17)

- a) keeping tissue viable
- b) preventing autolysis
- c) facilitating tissue processing
- d) dissolving calcium from bone
- e) preventing growth of saprophytes

**Ans.** a) T b) T c) T d) F e) T

**Q. Fixatives are used to** (BSMMU – Residency - MD, MS, Basic Science, Dentistry - March' 17)

- a) keep the tissue viable
- b) prevent autolysis
- c) facilitate tissue processing
- d) enhance H&E staining
- e) dissolve calcium in bony tissue

**Ans.** a) T b) T c) T d) T e) F

**Q. Chemicals used as tissue fixatives are** (BSMMU – Non-Residency – MD, MS, Basic science, Dentistry – July' 15)

- |                    |   |
|--------------------|---|
| a) alcohol         | T |
| b) normal saline   | F |
| c) formalin        | T |
| d) liquid paraffin | F |
| e) glycerine       | F |

**Q. Fixatives used in routine histo-pathological examination are** (BSMMU – Residency – MS – March' 16)

- |                       |   |
|-----------------------|---|
| a) 10% formalin       | T |
| b) 40% formalin       | F |
| c) Bouin's solution   | T |
| d) Hartman's solution | F |
| e) normal saline      | F |

**10% Formalin:**

- 10% Formalin (10% buffered formalin/ 10% neutral formalin)
- 40% formaldehyde must be mixed with 960 ml distilled water.
- Minimum strength

**Q. Autolysis of biopsy samples is prevented by (BSMMU – Residency – MD, MS, Basic – March' 15)**

- a) 10% formalin
- b) 10% formaldehyde
- c) freezing
- d) 10% dextrose
- e) glutaraldehyde

Ans. a) T b) F c) F d) F e) T

**Q. Fixatives used in cytology are (BSMMU – Residency – MD, MS, Basic Science – March' 15)**

- a) 95% ethanol
- b) commercial spray fixative
- c) glutaraldehyde
- d) 10% buffered formalin
- e) normal saline

Ans. a) T b) T c) F d) F e) F

**Q. Following chemicals / substances are used as fixative for biopsy/ cytology samples: (BSMMU – Non-Residency – MD/MS, Basic science – July' 14)**

- a) 95% alcohol
- b) xylene
- c) 10% formalin
- d) liquid paraffin
- e) normal saline

Ans. a) T b) F c) T d) F e) F

**Q. The following chemicals can be used as fixatives for biopsy samples (BSMMU – Residency – MD/MS, Basic science – March' 14)**

- |                          |   |
|--------------------------|---|
| a) normal saline         | F |
| b) Zenker's solution     | T |
| c) Bouin's solution      | T |
| d) 10% buffered formalin | T |
| e) paraffin wax          | F |

**Q. Preservatives are used after biopsy to: (BSMMU – Residency – MD/MS – March' 13)**

- a) Process the tissue for microtome sectioning
- b) Prevent autolysis
- c) Proceed for bacterial culture
- d) stabilized tissue architecture
- e) Prevent bacterial growth

Ans : a) T b) T c) F d) T e) T

**Q. 10% Formalin solution: (BSMMU – M. Phil, Diploma (Non-Residency)–March-2012, DMC & others – MD/MS – March-2012)**

- a) is an irritant agent for eyes
- b) is a colourless fluid
- c) prevents autolysis of biopsy samples
- d) is used as a fixative for cytology samples
- e) should be used for sending frozen section samples

Ans. a) T b) T c) T d) F e) F

**Q. The following substances are used as fixative for biopsy samples: (BSMMU - M. Phil, Diploma – July '10)**

- |                  |   |
|------------------|---|
| a) 1% formalin   | F |
| b) 90% ethanol   | F |
| c) 10% formalin  | T |
| d) normal saline | F |
| e) savlon        | F |

**Q: The solutions used as fixatives for pathological specimens are** (ESMMU – MD – January, 2010)

- a) 10% formalin
- b) 40% formaldehyde gas
- c) 95% ethanol
- d) Normal saline
- e) Liquid paraffin

## Staining

### Staining (Histo):

- Routine staining: Hematoxylin & eosin
- Special staining:
  - PAS – Glycogen--confirm by diastase.
  - Congo red stain- Amyloid (apple green)
  - Reticulin stain- reticulin fibre & basement membrane
  - Trichrome stain- muscle, collagen, fibre, erythrocyte
  - Perl's prussian blue- Hemosiderin
  - Masson fontana- Melanin
  - Von kossa- Calcium

### Amyloid stain

- Congo red
  - Methyl violet
  - Crystal violet
  - Thioflavin T
  - Thioflavin S
- Colour: Apple green birefringence
  - Polarized microscope needed

### Special stain for CHO & Lipid:

#### For CHO:

- Best's carmine
- PAS
- Alcian blue
- Mucin stain

#### For Lipid:

1. Oil red O
2. Sudan black B

**TABLE 8-2 – Special Techniques for Diagnosing Infectious Agents**

<b>Techniques</b>	<b>Infectious Agents</b>
Gram stain	Most bacteria
Acid-fast stain	Mycobacteria, nocardiae (modified)
Silver stains	Fungi, legionellae, pneumocystis
Periodic acid-Schiff	Fungi, amebae
Mucicarmine	Cryptococci
Giemsa	Campylobacteria, leishmaniae, malaria parasites
Antibody probes	All classes
Culture	All classes
DNA probes	All classes

**Staining (cyto)**

- Routinely: Papanicolaou stain
- Others:
  - H & E
  - Gram stain
  - Z-N stain
  - Giemsa
  - PAS
  - Oil red O
  - Sudan black

**Biopsy**

**Definition:** Biopsy is the process of collection of tissue from living body for histopathological examination.

**Types of biopsy/ Techniques of tissue sampling:****A. Open biopsy:**

1. Incisional biopsy
2. Excisional biopsy
3. Frozen section biopsy.

**B. Closed biopsy**

1. FNAC (Fine needle aspiration cytology)
2. True-cut needle biopsy
3. Punch biopsy
4. Loop biopsy
5. Endoscopic suction biopsy with brush cytology for upper GIT - Gastroscope washout; Exfoliative cytology of bronchial wash out; Urinary sediment, etc.
6. Image guided biopsy.

**A. Open biopsy**

**1. Incisional biopsy-** Incisional biopsy by taking a part or wedge of the session (ulcer or tumour) including the margin and normal surrounding skin tissue (important for histological comparison). Wedge biopsy for larger lesion more than 5cm of diameter. It is usually done in outpatient clinic or ward under local anaesthesia.

**2. Excisional biopsy-** Excisional biopsy by taking the entire lesion with safety skin or tissue margin. It is usually done in OT under GA. Example- Lymph node biopsy, Orchidectomy, etc.

**3. Frozen section biopsy-** Frozen section biopsy is an open excisional biopsy, which is done when quick diagnosis is required (within 10- 15 minutes) for a definitive treatment. E.g. Breast lump, etc.

**B. Closed biopsy:**

**1. FNAC (Fine needle aspiration cytology):** FNAC is a minimal invasive process of cytological study of palpable superficial lump. FNAC is done by aspiration of fluid or solid masses by using a fine gauge needle (21-23G; Average: 22G). Deep seated lump and lesion may also be studied under the guidance of USG and CT scan, For example-

- a. Breast lump
- b. Enlarged lymph node
- c. Thyroid swelling
- d. Parotid swelling
- e. Subcutaneous lesion (lipoma), etc.

**2. Tru-cut needle biopsy /core needle biopsy:** Core biopsy or tru-cut needle biopsy is percutaneous biopsy for histopathological study of superficial palpable lump. Deep seated and impalpable lump may also be studied by core biopsy under the guidance of fluoroscopy, USG or CT scan.

For example-

- a. Most common for soft tissue mass
- b. Breast lump
- c. Prostate lesion
- d. Pleural biopsy
- e. Liver biopsy, etc.

**3. Punch biopsy:** Punch biopsy is done in outpatient clinic, ward or theatre for instance a punch biopsy of rectal polyp via rigid sigmoidoscope/ Punch biopsy of Ca- stomach during endoscopy.

**4. Loop biopsy-** e.g. TUR prostate (TURP)

**5. Endoscopic suction biopsy** e.g.

- a. Brush cytology for upper GIT- gastroscope washout
- b. Exfoliative cytology of bronchial washout
- c. Urinary sediment, etc.

**6. Image guided biopsy:** Biopsy under the guidance of fluoroscopy, USG or CT scan imaging, e.g. Biopsy from retroperitoneal mass.

**Principle or rules of biopsy:**

1. The larger the lesion the greater the number of biopsies.
2. For ulcerated lesion, central necrotic area should be avoided, where margin and surrounding normal skin tissue should be included.
3. To assess the depth of lesion and relationship with the surrounding tissue (staging), a deep and whole thickness of lesion should be taken.
4. Crushing or damage of the histopathological features should be avoided (gentle handling of tissue by minimal grasping)
5. Tissue should be immediately placed into the container, containing adequate volume of fixatives.
6. The container containing biopsy material should be labeled with particulars of the patient (Name, Age, sex, Reg. no., Bed no., etc.)

7. Requisition of histopathological examination should be included with brief history along with physical findings.

**NB: Commonly used fixatives-**

1. 10% buffered formalin- the dual fixative
2. Zenker's solution- for kidney, testes, lymph node, bone marrow, etc.
3. Carnoy's fixative- for lymph node
4. Chromate solution- for chromaffinoma
5. Glutaraldehyde solution - for electron microscopy.

**Question Bank**

**Q. A biopsy is suitable for proper histological assessment if (BSMMU – Non-Residency – MD, MS, Basic science – July' 16)**

- |  |   |
|--|---|
| a) it is autolysed                     | F |
| b) normal margins are included         | F |
| c) frozen for preservation             | F |
| d) preserved in 10% alcohol            | F |
| e) accompanied by clinical information | T |

**Q. Tru-cut biopsy is suitable in the evaluation of (BSMMU – Residency – MS, Basic Science – March' 16)**

- |                                      |   |
|--------------------------------------|---|
| a) breast lumps                      | T |
| b) liver masses                      | T |
| c) intro cranial lesions             | F |
| d) retroperitoneal tumors            | T |
| e) soft tissue sarcomas of the limbs | T |

**Q. A 25 years female has got a FNAC report of her left sided breast lump stated as “suspicious cytology”.**

**What next steps she should be advised ? (BSMMU – Residency – MD, MS, Basic Science – March' 15)**

- a) repeat FNAC
- b) biopsy
- c) frozen section
- d) mammography
- e) mastectomy

Ans. a) F b) T c) F d) F e) F

**Q. Frozen section biopsy is used in (BSMMU – Residency – MD/ Basic science – March' 14)**

- a) categorization of tumor as benign or malignant
- b) identification of organism in tissue
- c) identification of ganglion cell in Hirschsprung disease
- d) definitive diagnosis of a tumour
- e) to see resection margins of a malignant tumour

Ans. a) T b) F c) T d) F e) T

**Help Link:**

**Frozen section biopsy:** Frozen section biopsy is a type of open excisional biopsy, which is done when a quick diagnosis is required (within 10-15 minutes) for definitive treatment.

**Criteria of frozen section biopsy:**

1. Frozen section biopsy is done peroperatively (e.g. During mastectomy)
2. Pre arrangement between surgery team and the pathologist.
3. Skilled histopathologist should be required
4. Biopsy specimen is not immersed within the fixative and not embedded in paraffin.
5. Biopsy specimen is sent to the pathology within a dry container.
6. Pathologist informs the surgeon about the exact diagnosis over the phone in the theatre.

**Procedure:** The biopsy specimen is frozen at -25°C by using solid CO<sub>2</sub> or liquid nitrogen then the frozen tissue is sectioned in a specialized cabinet, containing microtome (cold knife). These sectioned tissues are then stained with H & E (Hematoxylin and Eosin) stain and examined under the microscope.

**Purpose/ objectives:**

1. It is a quick diagnostic procedure (within 10-15 minutes).
2. It is a peroperative diagnostic procedure, so definitive treatment or first look operation can be done.
3. It has high accuracy rate with low false positive and false negative results.

**Disadvantages:**

1. Interpretation is more difficult than in fixed paraffin section.
2. Skilled histopathologist is required.
3. Pathologist needs brief history and clinical findings about the patient.

**Q. Frozen section is indicated in:** (BSMMU – Residency – MD/MS – March'13)

- a) Intra-operative categorization of tumour as benign or malignant
- b) Intra-operative diagnosis of Hirschsprung's disease
- c) Categorization of malignant tumours
- d) Scoring of hepatic inflammation
- e) To see the resection margins of a malignant tumour whether free or involved

Ans: a) T b) T c) F d) F e) T

**Q. Frozen section is done:** (BSMMU – M. Phil, Diploma (Non-Residency)–March-2012, DMC & others – MD/MS – March-2012)

- |  |   |
|--|---|
| a) to see surgical margins of a malignant tumour           | T |
| b) to see ganglion cells in suspected Hirschsprung disease | T |
| c) peroperatively  | T |
| d) to categorize malignant tumour                          | F |
| e) for immunohistochemistry                                | T |

**Q. Frozen section is useful because it:** (BSMMU – MD/MS – January, 2010)

- |  |   |
|--|---|
| a) is cheap                                | F |
| b) can predict malignancy during operation | T |
| c) preserves tissue substances like fat    | T |
| d) is more accurate than routine section   | F |
| e) can replace routine section             | F |

### Fine needle aspiration cytology (FNAC)

**Fine needle aspiration cytology (FNAC):**

**Definition:** FNAC is minimally invasive technique for cytological study of superficial palpable lump. It is done by aspiration of fluid and cells from mass by a fine gauge needle (21-23 G; Average: 22G). Cytological study of deep seated lesion can also be done by FNAC under the guidance of fluoroscopy, USG or CT scan imaging.

**Technique of FNAC:**

1. **Collection-** with all aseptic precaution a 10-20 ml plastic syringe with a 22G needle is inserted into the skin overlying the suspected mass under local anaesthesia. After passing through the mass a suction is applied; Hence needle is passed in 3 to 4 direction within the mass and suction is applied each time. Then the needle is withdrawn and syringe contents blown out on the glass slide.
2. **Preparation of cytology smear-** The specimen on the glass slide dried in air and then fixed with ethanol or carbowax (Polyethylene glycol-PEG).
3. **Staining-** Common stains are Giemsa stain, H & E (Hematoxylin and eosin stain) stain and Papanicolaou stain.
4. **Microscopic examination** - Examination under microscope.

**Applications of FNAC:**

1. Breast lump
2. Enlarged lymph node
3. Thyroid swelling
4. Parotid swelling
5. Subcutaneous lesion (lipoma)
6. Modern advancement- Image guided FNAC.

**Advantages of FNAC:**

1. The technique is relatively painless, produces a speedy result and is cheap.
2. FNAC saves the costly days in hospital, since a tissue diagnosis can be obtained within minutes rather than days.
3. The low risk of complications is an additional advantage which allows fine-needle aspiration biopsy to be performed as an office procedure in out patient department. -
4. It is highly suitable for debilitated person.
5. It is readily repeatable and useful for multiple lesions.
6. Another advantage of FNA biopsy is that aspiration can be done without anaesthesia.

**Disadvantages:**

1. False negative due to faulty sampling
2. Staging can't be done, because only cellular architecture is found.
3. FNAC can't distinguish between follicular adenoma and follicular carcinoma of thyroid, because it can't reveal the extent of invasion of the tumour.
4. Less reliable in cystic swelling.

**Question Bank**

**Q. FNAC is done for the diagnosis of (BSMMU – Residency – MD/MS, Basic science, Paediatrics, Dentistry – March '15)**

- a) tubercular lymphadenitis
- b) hemangioma of liver
- c) papillary carcinoma of thyroid
- d) cystadenocarcinoma of ovary
- e) stromal invasion of a tumor

Ans. a)T b) T c) T d) T e) F

(Ref. Bancroft laboratory techniques)

**Q. Image guidance is needed for FNAC of following organs (BSMMU – Residency – MD, MS, Basic Science – March '15)**

- a) breast lump
- b) chest wall swelling
- c) space-occupying lesion of liver
- d) cervical lymph node
- e) para-aortic lymph node

Ans. a) F b) F c) T d) F e) T

**Help link:**

**Image guided FNAC** (Fine needle aspiration cytology) is an interventional radiological procedure which is applicable to most radiologically detectable abnormalities.

**Principles of (FNAC) image guided FNAC:**

1. In general the shortest route from skin to lesion is chosen, if no vital structures intervene.
2. Fluoroscopy usually provides suitable guidance for biopsy of large parenchymal or perihilar mass in the chest → under the guidance of fluoroscopy.
3. USG and CT scan is used in small lesions in the retroperitoneum and abdomen → under the guidance of USG.
4. 22G needle is used for FNAC.

**Contraindications:** There are no absolute contraindications but some relative contraindications are-

1. Lesion immediately adjacent to blood vessels.
2. Intraabdominal lymph node biopsy
3. Biopsy path that traverse the colon.
4. Carcinoma head of pancreas
5. Carcinoma of liver
6. Bronchogenic carcinoma
7. Mediastinal tumour, etc.

**Complications:**

1. Bacteraemia
2. Septicaemia
3. Haemorrhage
4. Pancreatitis
5. Pneumothorax
6. Tumour seedling in the needle track.

**Q. A 25 years female has got a FNAC report of her left sided breast lump stated as "suspicious cytology".**

**What next steps she should be advised ? (BSMMU – Residency – MD, MS, Basic Science – March' 15)**

- a) repeat FNAC
- b) biopsy
- c) frozen section
- d) mammography
- e) mastectomy

Ans. a) F b) T c) F d) F e) F

**Q. Fine needle aspiration cytology (FNAC) is not suitable for the diagnosis of: (BSMMU – Residency – MD/MS – March' 13)**

- a) Follicular non-Hodgkin lymphoma
- b) Nodular sclerosis Hodgkin lymphoma
- c) Axillary lymph node metastasis
- d) Fibromatosis
- e) Lymph node tuberculosis

Ans : a) T b) T c) F d) T (because it is an intermediate grade tumour, diagnosed by biopsy) e) F  
(commonly diagnosed by FNAC)

**Q. The following are the examples of samples for cytology examination: (BSMMU – Residency – MD/MS – March' 13)**

- a) Sputum
- b) Scraping from oral ulcer
- c) Endoscopic biopsy
- d) Core needle biopsy
- e) Urine

Ans : a) T b) T c) F d) F e) T

**Q. Fine needle aspiration cytology (FNAC) (BSMMU – MD/MS (Residency) – January, 2011)**

- |  |   |
|--|---|
| a) is a better method of tumour diagnosis than histopathology. | F |
| b) is less expensive as a test                                 | T |
| c) is not suitable for deep seated tumours.                    | F |
| d) can be performed by nurses                                  | F |
| e) is suitable for detection of metatasis in lymph nodes       | T |

**Q. Fine needle aspiration cytology (FNAC) – (BSMMU – MD/MS - January, 2009)**

- |   |   |
|---|---|
| a) Carries little risk of mortality and morbidity | T |
| b) Is an expensive diagnostic procedure           | F |
| c) Is more informative than biopsy                | F |
| d) Can be done at out patient departments         | T |
| e) Is useful in evaluating lymph node metastasis  | T |

## Exfoliative cytology

**Q.** Exfoliative cytology is useful for the diagnosis of (BSMMU – Residency – MD, MS, Basic science, Dentistry – March '16)

- a) meningioma
- b) multiple myeloma
- c) bladder cancer
- d) bronchial cancer
- e) cervical cancer

Ans.

- a) **False** The examination of cerebro-spinal fluid for exfoliated cells has not been shown to be particularly useful in the diagnosis of tumors of the CNS. Meningiomas do not generally shed cells into the CSF.
- b) **False** Although malignant plasma cells may be demonstrated occasionally in the peripheral blood in patients with multiple myeloma, this cannot strictly be called exfoliative cytology. Malignant cells in this condition are usually sought in marrow specimens.
- c) **True** Exfoliative cytology is used extensively for the exclusion or diagnosis of tumors of the bladder. It is also extensively used in the screening of asymptomatic individuals working in the aniline dye industry.
- d) **True** Malignant cells can be demonstrated in the sputum, bronchial washings and if present, in a pleural effusion, in patients suffering from bronchial cancer.
- e) **True** Vaginal and cervical smears are commonly used to eliminate or confirm a diagnosis of carcinoma of the cervix or uterus. The abnormal cells which are pleomorphic and hyperchromatic are demonstrated by the use of a 'Papanicolaou' smear. This technique may also identify carcinoma in situ and various forms of dysplasia.

(Ref. Robbins-9<sup>th</sup>, P-333; Smiddy)

### Help link:

When cancer involves a lining epithelium, some of the neoplastic cells are shed onto the surrounding surface. If the surface is internal, these cells are trapped in the secretion of the part and ultimately discharged to the exterior. This approach is widely used to detect carcinoma:

- carcinoma of the cervix, often at an in situ stage. (*cervical carcinoma cells may be shed into the vaginal secretions*)
- endometrial carcinoma,
- bronchogenic carcinoma, (Bronchial carcinoma cells may be coughed up in the sputum)
- bladder and prostatic tumors,
- gastric carcinomas; (gastric carcinoma cells may be aspirated in the gastric juice)
- for the identification of tumor cells in abdominal, pleural, joint, and cerebrospinal fluids; and,
- less commonly, with other forms of neoplasia.

(Ref: Robbin's & Cotran's-9<sup>th</sup>, P-333)

**Q.** Exfoliative cytology has a diagnostic role in detection of (BSMMU – Residency – MS, Basic Science – March '15)

- a) bronchogenic carcinoma
- b) transitional cell carcinoma
- c) renal cell carcinoma
- d) carcinoma cervix
- e) esophageal carcinoma

Ans. a) T b) T c) F d) T e) T

**Q.** Exfoliative cytology may play role in the diagnosis of the following malignant disorders (BSMMU – Residency – MS, Basic science – March '14)

- a) bronchogenic carcinoma
- b) malignant urothelial tumors
- c) cervical cancer
- d) gastric cancer
- e) sino nasal cancer

**Ans.**

- a) **True** Malignant cells can be demonstrated in the sputum, bronchial washings and if present, in a pleural effusion, in patients suffering from bronchial cancer.
- b) **True**
- c) **True** Vaginal and cervical smears are commonly used to eliminate or confirm a diagnosis of carcinoma of the cervix or uterus. The abnormal cells which are pleomorphic and hyperchromatic are demonstrated by the use of a Papanicolaou smear. This technique may also identify carcinoma in situ and various forms of dysplasia.
- d) **True**
- e) **False**

**Q. Exfoliative cytology is useful for the diagnosis of (BSMMU – Residency – Dental surgery – March' 14; M-Phil. Diploma, July' 05)**

- A. Meningioma.
- B. Bronchial cancer
- C. Multiple myeloma
- D. Cervical cancer
- E. Vesical cancer

**Ans.**

- A. **False** The examination of cerebrospinal fluid for exfoliated cells has not been shown to be particularly useful in the diagnosis of tumors of CNS. Meningiomas do not generally shed cells into the CSF.
- B. **True** Malignant cells can be demonstrated in the sputum, bronchial washings and if present, in a pleural effusion, in patients suffering from bronchial cancer.
- C. **False** Although malignant plasma cells may be demonstrated occasionally in the peripheral blood in patients with multiple myeloma, this cannot strictly be called exfoliative cytology. Malignant cells in this condition are usually sought in marrow specimens.
- D. **True** Vaginal and cervical smears are commonly used to eliminate or confirm a diagnosis of carcinoma of the cervix or uterus. The abnormal cells which are pleomorphic and hyperchromatic are demonstrated by the use of a Papanicolaou smear. This technique may also identify carcinoma in situ and various forms of dysplasia.
- E. **True** Exfoliative cytology is used extensively for the exclusion or diagnosis of tumors of the bladder. It is also extensively used in the screening of asymptomatic individuals working in the aniline dye industry.

**Q. Exfoliative cytology (MD/MS (DMC)-02Ja)**

- |   |   |
|---|---|
| a) Involves the study of wax-embedded pieces of tissue.   | F |
| b) Is performed on cells aspirated through a fine needle. | F |
| c) Is used to screen for carcinoma of the uterine cervix. | T |
| d) May be used to diagnose carcinoma of the bronchus.     | T |
| e) Is often used in the diagnosis of breast lesion.       | F |

### Immunohistochemistry

**Q. Immunohistochemistry is employed to (BSMMU – Residency – MD, MS, Basic Science – March' 15)**

- a) distinguish neoplastic from non-neoplastic lesion
- b) distinguish benign from malignant lesion
- c) localize the cell of origin of tumour
- d) detect auto-antibodies in the serum
- e) distinguish primary from metastatic cancer.

Ans. a) F b) F c) T d) F e) T

**Help link:**

#### Immunohistochemistry:

It is a technique for identifying cellular or tissue Ag by means of Ag-Ab reactions, the site of Ab binding being identified by direct labeling of the Ab or by the use of a second labeling method.

The Ag-Ab reactions are visualized by the use of a self coloured substrate or chromogen (dab means diaminobenzene which is pink or brown colour).

Ab may be monoclonal or polyclonal.

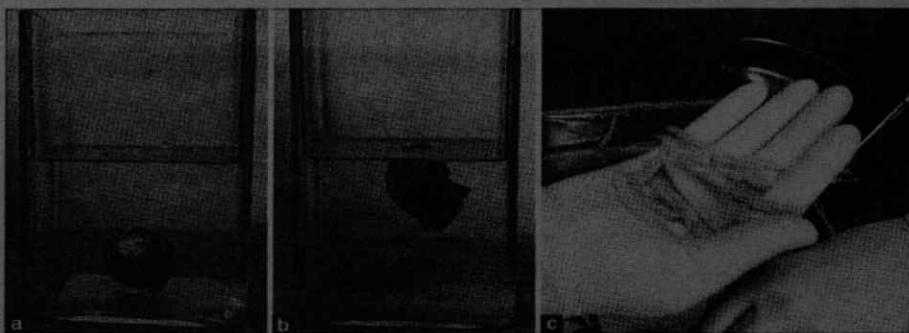
#### Use/ applications:

1. **Determination of origin of tumour** by the presence or absence of
  - a) Intermediate filaments - are the cytoskeletal component of both normal and tumour cells.
    - cytokeratin (favours epithelial origin carcinoma), vimentin, desmin (for muscle cell origin), neurofilament, s-100 (glial fibrillary acid protein)
  - b) Other epithelial marker: Epithelial membrane Ag, tumour marker, neuron specific enolase.
  - c) Mesenchymal: Myoglobin, actin
  - d) wbc series: cla (cd 45) (cla means common leukocytic Ag)
2. **Can detect invasion of carcinoma:** by Ab against collagen 4 and laminin i.e basement membrane component in breast carcinoma by Ab against myoepithelial cells.
3. **In metastasis:** can be used for occult/ micrometastasis in lymph node or bone.
4. Can distinguish between reactive hyperplasia with lymphoma. In hyperplasia lymphocytic population is polyclonal, in lymphoma it is monoclonal.
5. **Therapeutic response:** Receptor protein identified to asses how the tumour will response to hormone i.e ca breast.
6. **Tumour aggressiveness:** by cell proliferation marker.
7. **Infectious disease:** HBV, H. Pylori, Cryptococcus

(Ref: Robins-9<sup>th</sup>, P-334 + Bancroft)

## Decalcification

- Hydroxyapatite crystals removed from bone
- Reagents:
  - a) **Acid:**  
HNO<sub>3</sub> (5 %): rapidly decalcify, tissue damage more if more than 2 days kept in acid or conc.  
Is more than 8 %,  
HCL, formic acid, trichloroacetic acid
  - b) **EDTA**



## GENETICS

- ❖ **Heredity/ Inheritance:** process of transmission of character from one generation to next.
- ❖ **Gene:** fundamental units of inheritance, determines the character
- ❖ **Genetics:** study of genes and of the statistical laws that passage from one generation to next.
- ❖ **Single gene disorder:** problem is single gene, follow Mendelian inheritance, eg: AD, AR, X-linked.
- ❖ **Multifactorial disorder:** additive effects of multiple gene. eg: interaction of gene with environmental factors.

### **Human chromosome**

- Number of chromosome is constant
- Each human somatic cell is 46 number of chromosome(diploid or  $2n$ )
- Number of chromosome in ova or sperm 23 or  $n$ .
- 44 number autosome, 2 sex chromosome
- Male- 44+XY, female-44+XX
- Size: visible when cell is mitotic or meiotic cell division, average size of metaphase chromosomes 5 micron meter.
- Shape: V or rod or J shaped
- **Structure:** short arm is p, long arm is q.
- **Centromere:** responsible for movement of chromosome at cell division, specific and essential region, visible after condensation, consists of DNA and proteins, spindle fibres are attached, in anaphase, centromere divides longitudinally, two sister chromatids move opposite poles.
- **Telomere:**
  - ✓ ends of chromosome made of special DNA,
  - ✓ essential structures,
  - ✓ provides structural stability by sealing both ends,
  - ✓ protects both ends from damage, fusion with other,
  - ✓ do not contains the codes for proteins, so, they are not genes.

### **Genes:**

- 30,000 genes located on 23 pairs of chromosomes
- Function: the synthesis of protein(made up of polypeptide chain from different amino acid)
- The vast amount of DNA sequences are transcriptionally inactive
- Those do not act as a gene called junk DNA/ extragenic DNA/ repetitive DNA sequence
- **Genic DNA:** single or low copy number of DNA sequence
- **Extragenic:** highly repetitive DNA sequence
  1. **Tandemly repeated DNA sequence:**
    - satellite DNA(near centromere)
    - Minisatellite (telomeric DNA)
    - Microsatellite (highly variable DNA sequences, forms the basis of DNA finger printing, sequences are present throughout the genome)
  2. **Interspersed repeated DNA sequence**

**Genetic code:**

- Three bases on DNA strand codes for one AA.
- Triplet code: genetic information(code) is stored in the form of three bases determining one AA.
- During the process of transcription triplet code is transferred from DNA to mRNA.
- Initiation code is AUG, termination code is UAA or UAG.
- It is same for all kinds of living organisms
- It is universal
- Eg: human insulin by E. coli bacteria,
- Change of arrangements of bases, leads to defective proteins.

**Mutation**

1. **Point mutation:** if changes occur in structure of a gene
  - a. Substitutional mutation, eg: sickle cell anaemia
  - b. Frame shift mutation, eg: insertion or deletion.
2. **Chromosomal mutation (lethal mutation):** if changes in chromosomal structural or numerical.
  - Without mutation a species can not acquire new genes which is necessary for adaptive change
  - It provides raw material for evolution
  - Most mutations are harmful.

**Disorders of chromosomal structures:**

- **Deletion:**
  - ✓ **Microscopic deletion**, eg: deletion in short arm of chromosome 5(cri-du-chat syn), chromosome 4(wolf-Hirschhorn syndrome)
  - ✓ **Submicroscopic deletion**, not visualized by karyotyping, needs FISH,
  - ✓ eg: prader willi, angelman, wilm's tumour, williams, Di-george Syn, smith-magenis syndrome.
- **Inversion:**
  - ✓ pericentric and paracentric, not responsible for any clinical problems in carriers,
  - ✓ no chromosomal material is lost, produce abnormal gamete during meiosis-1,
  - ✓ causes spontaneous abortion or abnormal offspring
- **Ring chromosome:**
  - ✓ entire chromosome may be lost,
  - ✓ r usually chromosomal mosaic.
- **Isochromosome**, incorrect splitting of centromere, duplication of one entire chromosome arm and a deletion of the other chromosome arm.
- **Translocation:**
  - may be balanced or unbalanced, carriers are normal, but their children may be physically and mentally handicapped.
  - Reciprocal, usually balanced, eg: between 11 and 22, in CML 9 and 22/ABL+BCR called philadelphia chromosomes.
  - Robertsonian- short arm of both chromosomes are lost, eg: commonly 13 and 14 number of chromosomes,
  - Down syndrome (4 %), two normal 21 chromosomes and one translocated chromosomes at 21 number. 14q21q.
  - It is due to X-ray, chemical and viral infection

**Philadelphia chromosomes:**

- Acquired chromosomal abnormality
- Found in 85 % of CML
- Problem in 9 and 22 no. of chromosomes
- Prognosis is worse if it is absent
- Also reported in – myelofibrosis and polycythaemia rubra vera.

**Mosaic or mosaicism:**

Two different cell lines from a single zygote, some cells may be normal (46,XX/XY), others have extra chromosomes (47, XX or XY)

- E.g: male mosaic- 46, XY/47, XY

**Chimerism:** two or more distinct cell lines are derived from more than one zygote.

e.g: true hermaphrodite.

**Non-dysjunction:** Failure of the homologous pair of chromosomes to separate during meiosis.**Causes of non-dysjunction:**

- Advancing maternal age
- Radiation
- Delayed fertilization after ovulation
- Chemicals in the environment – smoking, alcohol consumption, oral contraceptives, fertility drugs, pesticides etc.
- Genetic cause

**Maternal age also affects:**

- Hydrocephalus
- Anencephaly
- Achondroplasia(also in paternal age)

**Types of chromosomal mutation:** 50% of spontaneous abortion, and 0.5-1 % of all newborn infants**1. Numerical**

- a. Aneuploidy(gain or loss of one chromosome)
  - i. Monosomy
  - ii. Trisomy
  - iii. Tetrasomy
- b. Polyploidy(addition of more than 1 haploid chromosome)
  - i. Triploidy
  - ii. tetraploidy

**2. Structural**

- a. Translocation,
  - i. eg: Burkitt's lymphoma(from 8 to 14 no chromosome)
  - ii. Reciprocal
  - iii. Robertsonian
- b. Deletion (loss of more than one nucleotide): wilm's tumour(deletion of chromosomes 11)
- c. Insertion: (addition of more than one nucleotide)
- d. Inversion

3. Different cell line (mixploidy):

- a. Mosaicism,
- b. chimerism.

**Sex chromosomal disorder**

- Turner's syndrome(ovarian dysgenesis)-45 XO
- Noonan's syndrome- 45XY
- Testicular feminization syndrome(androgen insensitivity)-46 XY
- Klinefelter syndrome(seminiferous tubule dysgenesis)- 47XXY, XXXYY, or XXYY
- 47XYY- common in prison community
- Fragile X syndrome- most common cause of mental retardation
- Chromosomal breakage syndrome
- Triple X syndrome-47XXX, fertility normal.

**Numerical abnormality in autosomes**

- Trisomy 21- Down syndrome
- Trisomy 13- Patau's syndrome
- Trisomy 18 -Edwards syndrome

**Causes of trisomy 21 (Down syndrome)**

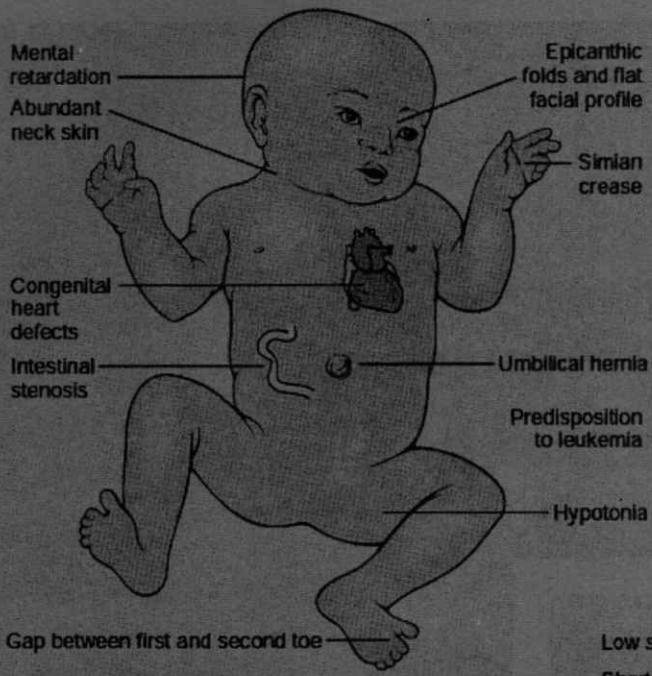
- Non-dysjunction- 94%
- Mosaicism- 2%
- Robertsonian translocation-4 %(in parents chromosomes)

**Turner syndrome**

- Cause:
  - Non-dysjunction,
  - Mosaicism (XO/XX, XO/XY, XO/XXX)

**Klinefelter syndrome (seminiferous tubule dysgenesis)**

- Karyotype: 47XXY, XXXYY, or XXYY
- One or two barr body/sex chromatin body

**TRISOMY 21: DOWN SYNDROME**

Incidence: 1 in 700 births

Karyotypes:

Trisomy 21 type: 47,XX, +21

Translocation type: 46,XX,der(14;21)(q10;q10),+21

Mosaic type: 46,XX/47,XX, +21

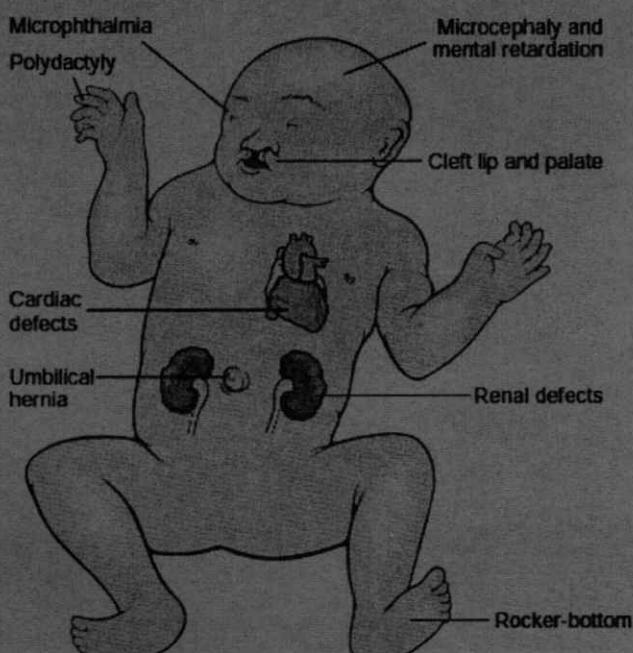
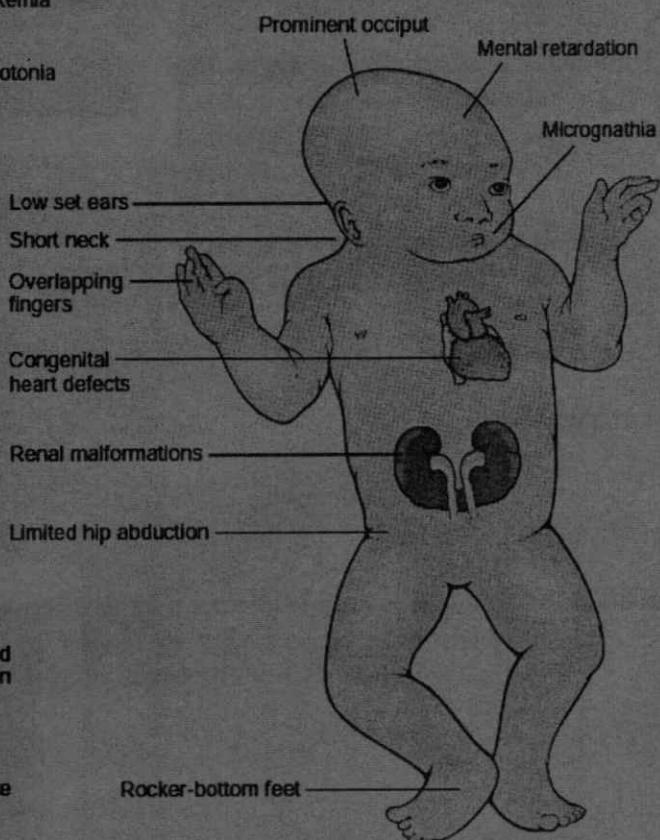
**TRISOMY 18: EDWARDS SYNDROME**

Incidence: 1 in 8000 births

Karyotypes:

Trisomy 18 type: 47,XX, +18

Mosaic type: 46,XX/47,XX, +18

**TRISOMY 13: PATAU SYNDROME**

Incidence: 1 in 15,000 births

Karyotypes:

Trisomy 13 type: 47,XX, +13

Translocation type: 46,XX,+13,der(13;14)(q10;q10)

Mosaic type: 46,XX/47,XX, +13

**Question Bank**

**Q. Structural changes of chromosome are (BSMMU – Non-Residency – MD, MS, Paediatrics, Basic Science – July' 19)**

- a) deletion
- b) reciprocal translocation
- c) trisomy
- d) insertion
- e) aneuploidy

Ans. a) T b) T c) F (Numerical change) d) T e) F (Numerical change)

**Help Link:****Structural change of Chromosome:**

- Deletion (loss of more than one nucleotide): wilm's tumour (deletion of chromosomes 11)
- Insertion: (addition of more than one nucleotide)
- Inversion:
- Isochromosome
- Ring chromosome
- Translocation,
  - eg: Burkitt's lymphoma (from 8 to 14 no chromosome)
  - Reciprocal
  - Robertsonian

**Q. Genetic code is (BSMMU – Residency - MD/MS, Basic science – March' 14)**

- |                    |   |
|--------------------|---|
| a) ambiguous       | F |
| b) non-redundant   | F |
| c) non-overlapping | T |
| d) universal       | T |
| e) commaless       | T |

**Help link:**

**Genetic code:** Total genetic message embedded in the gene is called genetic code.

Or, Genetic code is a dictionary that gives the correspondence between a sequence of nucleotide bases & a sequence of amino acid.

Or, Three nucleotide base sequence (triplet) in m-RNA that act as code words for amino acids in the protein constitute genetic code.

**■ Properties of genetic code:**

1. **Specificity:** The genetic code is specific – that is, a specific codon always codes for the same amino acid.
2. **Universality:** For all living system the codons are same.
3. **Redundancy/ Degeneracy:** For one amino acid there are more than one codon. For example, Arginine is specified by six different codons.
4. **Non overlapping and Commaless:** The genetic code is non-overlapping and commaless - that is, the code is read from a fixed starting point as a continuous sequence of bases, taken three at a time. For example, ABCDEFGIJKL... is read as ABC/DEF/GHI/JKL... without any punctuation between the codons.

(Ref: Lippincott-5<sup>th</sup>, P-430)

**Q. The following statements regarding DNA are true: (BSMMU – Residency – MD – March'13)**

- a) Is found outside as well as inside the cell nucleus
- b) Is found in the nucleosomes
- c) Is found in papilloma virus
- d) Is replicated mostly during the prophase of the cell division
- e) Replicates simultaneously in all parts of the chromosome

Ans. a) T (mitochondria also) b) T c) T (HPV is a DNA virus) d) F (replication occurs in S phase of interphase)

e) T

(Ref. Janquiera-14th, P-58-59)

**Q. Regarding human chromosome:** (BSMMU – M.Phil, Diploma-July,10)

- a) haploid number is 23
- b) female somatic cells have one inactive 'X' chromosome
- c) telomere is the most constricted region
- d) 47 XY, +21 is an example of triploidy
- e) Y is not essential for male development

F  
T (called Barr body)  
F  
F (Trisomy)  
F

**HELP LINK:**

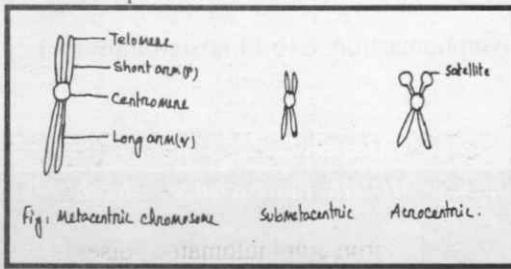
■ **Chromosome:** These are thread like structures located in the nucleus of the cells. It is made up of genes. In resting stage, they are seen as light granules or network of fibres under the microscope.

■ **Chromosome number:** In human, somatic cell nucleus contains 46 chromosomes (diploid), made up of 22 pairs of autosomes and one pair of sex chromosome (XY – in male, XX – in female).

In mature germ cell (sperm or ovum) contains 23 chromosomes (haploid)

■ **Classification of chromosomes:** Usually, there are 3 types of chromosomes according to the position of centromere:

1. Metacentric: Centromere is centrally placed.
2. Sub-metacentric: Centromere is intermediate in position.
3. Acrocentric: Centromere in terminal position.



Satellites are stock like appendages which are present only in acrocentric. It contains numerous genes of ribosomal RNA.

■ **Function of centromere:** It is very important, because it is responsible for the movement of chromosome during the cell division.

**■ Functions of chromosome:**

1. It carries genetic information.
2. It is responsible for growing & ageing process of cells.
3. Centromere helps in its movement during cell division.

**Autosomal dominant disorder, Autosomal recessive disorders & X-linked recessive disorders****Autosomal dominant disorder:**

System	Disorder
Nervous	Huntington disease Neurofibromatosis Myotonic dystrophy Tuberous sclerosis
Urinary	Polycystic kidney disease
Gastrointestinal	Familial polyposis coli
Hematopoietic	Hereditary spherocytosis von Willebrand disease
Skeletal	Marfan syndrome Ehlers-Danlos syndrome (some variants) Osteogenesis imperfecta Achondroplasia
Metabolic	Familial hypercholesterolemia Acute intermittent porphyria

(Ref: Robbins & Cotran-9<sup>th</sup>, P-141)

**Autosomal recessive disorders:**

System	Disorder
<b>Metabolic</b>	Cystic fibrosis Phenylketonuria Galactosemia Homocystinuria Lysosomal storage diseases $\alpha_1$ -Antitrypsin deficiency Wilson disease Hemochromatosis Glycogen storage diseases
<b>Hematopoietic</b>	Sickle cell anemia Thalassemias
<b>Endocrine</b>	Congenital adrenal hyperplasia
<b>Skeletal</b>	Ehlers-Danlos syndrome (some variants) Alkaptonuria
<b>Nervous</b>	Neurogenic muscular atrophies Friedreich ataxia Spinal muscular atrophy

(Ref: Robbins & Cotrans-9<sup>th</sup>, P-141)**X-linked recessive disorders:**

System	Disorder
<b>Musculoskeletal</b>	Duchenne muscular dystrophy
<b>Blood</b>	Hemophilia A and B Chronic granulomatous disease Glucose-6-phosphate dehydrogenase deficiency
<b>Immune</b>	Agammaglobulinemia Wiskott-Aldrich syndrome
<b>Metabolic</b>	Diabetes insipidus Lesch-Nyhan syndrome
<b>Nervous</b>	Fragile-X syndrome

(Ref: Robbins & Cotrans-9<sup>th</sup>, P-142)**COMMON MONOGENIC DISORDERS AFFECTING MAJOR ORGAN SYSTEMS:**

System	Disease	Inheritance
<b>Multisystem</b>	Neurofibromatosis	AD
	Tuberous sclerosis	AD
<b>Respiratory</b>	$\alpha_1$ -antitrypsin deficiency	AR
	Cystic fibrosis	AR
<b>Cardiovascular</b>	Hypertrophic cardiomyopathy	AD
	Long QT syndromes	AD and AR
<b>Renal</b>	Polycystic kidney disease	AD
	Alport's syndrome	XL
<b>Gastrointestinal</b>	Hereditary pancreatitis	AD
	Familial adenomatous polyposis coli	AD
<b>Hepatic</b>	Gilbert's disease	AD
	Haemochromatosis	AR
	Wilson's disease	AR
<b>Metabolic</b>	Phenylketonuria	AR
	Familial hypercholesterolaemia	AD

	Hypophosphataemic rickets	XLD, AD
<b>Endocrine</b>	Congenital adrenal hyperplasia	AR
	Multiple endocrine neoplasia	AD
	Kallmann's syndrome	XL or AD
<b>Haematological</b>	Sickle-cell disease	AR
	Alpha- and beta-thalassaemia	AR
	Haemophilia A and B	XL
<b>Neuromuscular</b>	Duchenne muscular dystrophy	XL
	Myotonic dystrophy	AD
	Spinal muscular atrophy	AR
<b>CNS</b>	Huntington's disease	AD
	Familial Alzheimer's disease	AD
	Friedreich's ataxia	AR
<b>Musculoskeletal</b>	Ehlers-Danlos syndrome	AD
	Marfan's syndrome	AD
	Osteogenesis imperfecta	Mostly AD
<b>Skin</b>	Albinism	AR
	Neurofibromatosis	AD
	Xeroderma pigmentosum	AR
<b>Eye</b>	Retinitis pigmentosa	AR, AD, XL
	Ocular albinism	XL

(Ref: Davidson-21<sup>st</sup>, P-60)**Question Bank****Q. X linked recessive traits are (BSMMU – Non-Residency – MD, Basic Science – July' 19)**

- a) phenylketonuria
- b) galactosemia
- c) Lesch-Nyhan syndrome
- d) Tay Sachs disease
- e) Hemophilia

Ans. a) F (AR)   b) F (AR)   c) T   d) F(AR- Lysosomal storage)   e) T

**Q. X-linked disorders are (BSMMU-Non-Residency-Paediatrics-july'19)**

- a) cystic fibrosis
- b) hemophilia
- c) Wilson disease
- d) acrodermatitis enteropathica
- e) Duchene muscular dystrophy

Ans. a) F (AR)   b) T   c) F (AR)   d) F (AR)   e) T

**Q. Autosomal dominant disorders are (BSMMU – Residency - MD, Basic science, Paediatrics, Dentistry – March '19)**

- a) Huntington's disease
- b) cystic fibrosis
- c) Marfan syndrome
- d) sickle cell anemia
- e) polydactyly

Ans. a) T   b) F(AR)   c) T   d) F (AR)   e) T

**Q. Autosomal dominant disorders are (BSMMU – Residency - Basic science – March' 19)**

- a) phenylketonuria
- b) poliposis coil
- c) achondroplasia
- d) cystic fibrosis
- e) Marfan's syndrome

Ans. a) F (AR) b) T c) T d) F (AR) e) T

**Q. Examples of autosomal recessive disorders are (BSMMU – Residency – MD, MS, Basic Science – March' 18)**

- a) familial hypercholesterolemia
- b) cystic fibrosis
- c) spinal muscular atrophy
- d) diabetes insipidus
- e) Duchenne muscular dystrophy

Ans. a) F b) T c) T d) F e) F

**Q. Autosomal dominant mode of transmission occurs in (BSMMU – Residency – MD – March' 18)**

- a) phenylketonuria
- b) hereditary spherocytosis
- c) Marfan's syndrome
- d) cystic fibrosis
- e) Huntington's disease

Ans. a) F b) T c) T d) F e) T

**Q. X-linked recessive disorders are (BSMMU – Residency - MD, MS, Basic Science - March' 17)**

- a) diabetes insipidus
- b) alkaptonuria
- c) polycystic kidney disease
- d) haemophilia
- e) Duchenne muscular dystrophy

Ans. a) T b) F c) F d) T e) T

**Q. X-linked disorders are (BSMMU – Non-Residency – MD, Basic science – July' 15)**

- a) myotonic dystrophy
- b) Duchenne muscular dystrophy
- c) Becker dystrophy
- d) Emery- Dreifuss dystrophy
- e) fascioscapulohumoral dystrophy

Ans. a) F (example of non-coding triplet repeat mutation) b) T c) T d) T e) F

**Q. Autosomal dominant disorders are (BSMMU – Residency – MD, MS, Basic Science – March' 15)**

- a) myotonic dystrophy
- b) tuberous sclerosis
- c) multiple sclerosis
- d) Friedreich's ataxia
- e) Duchenne's muscular dystrophy

Ans. a) T b) T c) F d) F e) F

**Q. Autosomal dominant diseases are (BSMMU – Residency - MD – March' 14)**

- |                               |   |
|-------------------------------|---|
| a) Wilson's disease           | F |
| b) Duchene muscular dystrophy | F |
| c) Becker muscular dystrophy  | F |
| d) myotonic dystrophy         | T |
| e) tuberous sclerosis         | T |

**Q. Following are the autosomal recessive disorders (BSMMU – Residency - MD – March' 14)**

- |                          |   |
|--------------------------|---|
| a) neurofibromatosis     | F |
| b) galactosemia          | T |
| c) mucopolysaccharidosis | T |
| d) haemophilia           | F |
| e) sydenham's chorea     | F |

**Q. Mode of inheritance is autosomal dominant in the following conditions: (BSMMU – Residency – MD – March'13)**

- |                       |   |
|-----------------------|---|
| a) Thalassaemia       | F |
| b) phenylketonuria    | F |
| c) Neurofibromatosis  | T |
| d) Hemophilia         | F |
| e) Tuberous sclerosis | T |

**Q. Autosomal recessive disorders are: (BSMMU – M. Phil, Diploma (Non-Residency)–March-2012, DMC & others – MD – March-2012)**

- |                         |   |
|-------------------------|---|
| (a) Diabetes mellitus   | F |
| (b) Haemophilia         | F |
| (c) Phenylketonuria     | T |
| (d) Hunter's syndrome   | F |
| (e) Huntington's chorea | F |

**Q. Autosomal dominant disorders are: (BSMMU – M. Phil, Diploma (Non-Residency)–11Ju, DMC & others – MD/MS – 11Ju)**

- a) Neurofibromatosis.
- b) All polycystic kidney diseases.
- c) Cystic fibrosis.
- d) Congenital adrenal hyperplasia.
- e) Achondroplasia.

Ans. a) T b) F (Adult polycystic is AD, Child polycystic is AR) c) F d) F e) T

**Q. The following are autosomal dominant disorders : (BSMMU – MD - January-11)**

- |                                   |   |
|-----------------------------------|---|
| a) neurofibromatosis              | T |
| b) polycystic kidney disease      | T |
| c) diabetes insipidus             | F |
| d) congenital adrenal hyperplasia | F |
| e) achondroplasia                 | T |

**Q. Autosomal recessive disorder are: (BSMMU – M.Phil, Diploma-July,10)**

- |                                |   |
|--------------------------------|---|
| a) Polycystic kidney disease   | F |
| b) Duchenne muscular dystrophy | F |
| c) Diabetes insipidus          | F |
| d) Marfan's syndrome           | F |
| e) albinism                    | T |

**Q. Autosomal recessive disorder are: (BSMMU – MD – January, 2010)**

- |                                   |   |
|-----------------------------------|---|
| a) thalassemia                    | T |
| b) phenylketonuria                | T |
| c) van willebrand's disease       | F |
| d) congenital adrenal hyperplasia | T |
| e) achondroplasia                 | F |

**Q. X-linked recessive disorders are:** (BSMMU - M. Phil, Diploma, July-09)

- |                                  |   |
|----------------------------------|---|
| a) Cystic fibrosis               | F |
| b) Conenital adrenal hyperplasia | F |
| c) Duchenne muscular dystrophy   | T |
| d) Chronic granulomatous disease | T |
| e) Diabetes insipidus            | T |

**Q. Following are the autosomal recessive disorder -** (DMC - MD/MS -09Ja)

- |   |   |
|---|---|
| a. galactosemia                                 | T |
| b. glucose 6 phosphate dehydrogenase deficiency | F |
| c. diabetis insipidus                           | F |
| d. $\alpha$ -antitrypsin deficiency             | T |
| e. vit. d resistant rickets                     | F |

**Q. Examples of autosomal dominant disorders are:** (BSMMU - M. Phil, Diploma, July-08)

- |                                   |   |
|-----------------------------------|---|
| a) neurofibromatosis              | T |
| b) haemochromatosis               | F |
| c) polycystic kidney disease      | T |
| d) congenital adrenal hyperplasia | F |
| e) Marfan's syndrome              | T |

**Q. The following disorders are transmitted in an autosomal dominant mode:** (BSMMU – MD/MS - January, 2008)

- |                      |   |
|----------------------|---|
| a) phenylketonuria   | F |
| b) polyposis coli    | T |
| c) achondroplasia    | T |
| d) cystic fibrosis   | F |
| e) Marfan's syndrome | T |

**Q. Autosomal dominant mode of inheritance is found in:** (M. Phil, Diploma (BSMMU) July, 2007)

- |                       |   |
|-----------------------|---|
| a) thalassaemias      | F |
| b) phenylketonuria    | F |
| c) haemophilia        | F |
| d) neurofibromatosis  | T |
| e) tuberous sclerosis | T |

**Q. Autosomal dominant inherited cancer syndrome include:** (BSMMU – Basic science, July-07)

- |                                   |   |
|-----------------------------------|---|
| a) Retinoblastoma                 | T |
| b) Xeroderma pigmentosum          | F |
| c) Familial adenomatous polyposis | T |
| d) Ataxia telangiectasia          | F |
| e) Carcinoma of breast            | F |

**Q. Autosomal recessive conditions:** (BSMMU – M. Phil, Diploma July, 2007)

- |                           |   |
|---------------------------|---|
| a) G-6 PD deficiency      | F |
| b) Achondroplasia         | F |
| c) albinism               | T |
| d) Haemophilia            | F |
| e) Hereditary spherotosis | F |

**Q. Following are autosomal recessive disorders:** (BSMMU – M. Phil, Diploma July, 2006)

- |                        |   |
|------------------------|---|
| a) Huntington's chorea | F |
| b) Hemophilia          | F |
| c) Phenylketonuria     | T |
| d) Cystic fibrosis     | T |
| e) Diabetes mellitus   | F |

**Q. Following disorders are transmitted by autosomal dominant mode:** (DMC – M. Phil, Diploma July, 2007)

- |                           |   |
|---------------------------|---|
| a) phenylketonuria        | F |
| b) familar polyposis coli | T |
| c) achondroplasia         | T |
| d) cystic fibrosis        | F |
| e) Marfans syndrome       | T |

**Q. Autosomal dominant inherited diseases are:** (DMC - MD/MS -06Ja)

- |                          |   |
|--------------------------|---|
| a. Tuberculous sclerosis | T |
| b. Neuro fibromatosis    | T |
| c. Wilson's disease      | F |
| d. Lesch-nyhan syndrome  | F |
| e. Marfan's syndrome     | T |

**Q. The followings are autosomal dominant:** (DMC – M. Phil, Diploma July, 2005)

- |                             |   |
|-----------------------------|---|
| a) Neurofibromatosis        | T |
| b) Huntington's disease     | T |
| c) Congenital spherocytosis | T |
| d) Sickle cell anaemia      | F |
| e) Beta thalassaemia        | F |

**Q. The following are autosomal dominant diseases:** (DMC - MD/MS -05Ja)

- |                             |   |
|-----------------------------|---|
| a) Neurofibromatosis        | T |
| b) Huntington's disease     | T |
| c) Congenital spherocytosis | T |
| d) Sickle cell anaemia      | F |
| e) Beta- thalassaemia.      | F |

**Q. Autosomal recessive inheritance occur in** (DMC - MD/MS -05Ja)

- |                      |   |
|----------------------|---|
| a) Haemophila        | F |
| b) Albinism          | T |
| c) Alkaptonuria      | T |
| d) Down's syndrome   | F |
| e) Neurofibromatosis | F |

**Q. Autosomal recessive inheritance occur in the following diseases:** (DMC - MD/MS -04Ja)

- |                                   |                        |
|-----------------------------------|------------------------|
| a) G-6-PD deficiency              | F (x-linked recessive) |
| b) Werdig-Hoffman disease         | T                      |
| c) Achondroplasia                 | F (autosomal dominant) |
| d) Congenital adrenal hyperplasia | T                      |
| e) Galactosaemia.                 | T                      |

**Q. Followings are the genetically transmitted diseases:** (DMC - MD/MS -04Ja)

- |                         |   |
|-------------------------|---|
| a) Huntington chorea    | T |
| b) Wilson's disease     | T |
| c) Multiple sclerosis   | F |
| d) Parkinson's disease  | F |
| e) Myotonia dystrophica | T |

**Q. Following genetic diseases are autosomal dominant** (M. phil, Diploma – 03Ju)

- |                              |   |
|------------------------------|---|
| a) Cystic fibrosis           | F |
| b) Neurofibromatosis         | T |
| c) Achondroplasia            | T |
| d) Spinal muscular dystrophy | F |
| e) Haembphilia B             | F |

**Q. Following genetic disorders are autosomal recessive- (DMC - MD/MS -03Ja)**

- |                                  |   |
|----------------------------------|---|
| a) Alkaptonuria                  | T |
| b) Familial hypercholesterolemia | F |
| c) Polycystic kidney disease     | F |
| d) Phenylketonuria               | T |
| e) Cystic fibrosis               | T |

**Q. Following disease have chromosomal abnormalities- (BSMMU-Sur-02Ju)**

- |                           |   |
|---------------------------|---|
| a) Turner's syndrome      | T |
| b) Klinefelter's syndrome | T |
| c) Achondroplasia         | F |
| d) Haemophilia            | F |
| e) Spina bifida           | F |

**Q. Autosomal recessive disorder include- (BSMMU-Sur-02Ju)**

- |                             |   |
|-----------------------------|---|
| a) Cystic fibrosis          | T |
| b) Sickle cell anaemia      | T |
| c) Hereditary spherocytosis | F |
| d) Beta thalassaemia        | T |
| e) Myotonic dystrophy       | F |

**Q. Following are autosomal recessive disorders- (BSMMU – MD/MS - 02Ja)**

- |                            |   |
|----------------------------|---|
| a) Phenylketonuria         | T |
| b) Familial polyposis coli | F |
| c) Von-willebrand disease  | F |
| d) Wilson disease          | T |
| e) Sickle cell anaemia     | T |

**Q. The following are X-linked recessive disorders- (BSMMU - MD - 01Ja)**

- |                                |   |
|--------------------------------|---|
| a) Diabetes insipidus          | T |
| b) Duchenne muscular dystrophy | T |
| c) Vit-D resistant rickets     | F |
| d) Wiskott Aldrich syndrome    | T |
| e) Sickle cell anaemia         | F |

**Q. The mode of transmission of the following genetic diseases are autosomal dominants: (DMC - MD/MS -01Ja)**

- |                                   |   |
|-----------------------------------|---|
| A. Duchenne muscular dystrophy.   | F |
| B. Hurler's syndrome.             | F |
| C. Familial hypercholesterolemia. | T |
| D. Wilson disease.                | F |
| E. Achondroplasia.                | T |

**Q. The following are autosomal dominant disorders- (BSMMU - M.Phil/ Diploma - 00Ju)**

- |                                   |   |
|-----------------------------------|---|
| a) Marfan's syndrome              | T |
| b) Phenylketonuria                | F |
| c) Alkaptonuria                   | F |
| d) Familial hypercholesterolaemia | T |
| e) Neurofibromatosis              | T |

**Q. The following are autosomal recessive disorders- (BSMMU - M.Phil/ Diploma - 00Ju)**

- |   |   |
|---|---|
| a) Galactosemia                                 | T |
| b) Glucose-6-phosphate dehydrogenase deficiency | F |
| c) Christmas disease                            | F |
| d) Congenital adrenal hyperplasia               | T |
| e) Multiple polyposis of colon                  | F |

## INHERITANCE

**Autosomal dominant disorders:** An autosomal dominant disorder is manifested even in the heterozygote state.

**Characteristics of Autosomal dominant disorders:**

Here the second copy of the gene on the homologous chromosome can not compensate for the mutated copy:

1. Consecutive generations are affected.
2. Half of offspring are affected. (50% of children are affected if an affected person marries a normal person).
3. Both males and females are equally affected (male = female)
4. Unaffected individual can not transmit diseases. (No carrier condition)
5. High new mutation rate

(Ref: Davidson + Basic MRCP)

**Characteristics of Autosomal recessive disorders:**

Here the second copy of the gene on the homologous chromosome compensates for the mutated copy:

1. Disease manifest only in homozygous state.
2. Heterozygotes are phenotypically unaffected.
3. Both males and females are equally affected
4. Unaffected carrier individuals transmit diseases.
5. If both parents are carriers, then one-quarter of their offspring are affected, and one-half are carriers. (siblings have one chance in four being affected)
6. Usually only one generation is affected.
7. The risk of each parent carrying the mutant gene is more in consanguineous marriage.

**X-linked dominant disorders:**

Here mutant gene is located on the sex chromosome. All sex linked disorders are X-linked.

**Characteristics of X-linked dominant disorders:**

1. Affects both sexes, but female more than males.
2. All children of affected homozygous females are affected.
3. Heterozygously affected female can transmit the disease to half their sons and half their daughters.
4. All daughters of affected males are affected but none of their sons.

(Ref: Basic MRCP + Davidson + Robbins-9<sup>th</sup>)

**Characteristics of X-linked recessive disorders**

1. Affected cases are usually males carrying the gene
2. A female may be affected if she is homozygous for the mutant gene due to affected father, and a carrier or affected mother.
3. Half the sons of carrier mothers affected and half the daughters are carriers.
4. No male to male transmission. Condition is transmitted by carrier women who produce affected boys, normal boys, carrier daughter, normal daughter.
5. Affected males can have only normal sons and carrier daughters.
6. Affected cases have affected brother and affected maternal uncles.

<b>Autosomal dominant</b>	<b>Autosomal recessive</b>	<b>X-linked dominant</b>	<b>X-linked recessive</b>
Male , female equally affected with the trait	Male and females are equally affected	Affects both sexes, but females are more	Males are affected, female are carrier., female will affected if presence of mutant homogzygous gene(rare).
Transmission between all sexes possible(gene autosome)	Seen in same generation among brothers and sisters siblings	No male to male transmission	Transmitted through unaffected carrier females to their sons.

Every generation affected without skipping	Does not seen in previous(parents) or subsequent generations(offspings), seen in only 4 <sup>th</sup> generation, not 3 <sup>rd</sup> or 5 <sup>th</sup> generation.	All children of affected homozygous females are affected. Affected case have affected brothers and affected maternal uncles.	Affected male do not transmit to their sons bcoz gene is not present in Y chromosomes.
Affected person have always an affected parents(if not then first time seen)	Risk increases if consanguinous marriage or first cousins	Affected male can transmit to all his daughters but none of his sons.  Female pass the trait to half their sons and half their daughters.	Affected male have normal parents(mutant X received from carrier mother)
New mutation occurs at the time of gametogenesis		Presence of mutant gene on X chromosomes	
Normal offspring do not transmit the disease(no carrier)	Carrier may present	Carrier may present	Carrier is present.
Heterozygous are phenotypically affected.	Homozygous are phenotypically affected(mutant allele in a double dose)	Expressed in heterozygous female and male	Recessive traits means genes are in double dose(homozygous) Heterozygous female transmit the disease, affected male transmit gene to all his daughter(carrier), and 50% of his grandsons .
Variable expressibility and anticipation.	Variable expressessivity is less problem		Traits are rare in females

**Question Bank**

**Q. Autosomal dominant inheritance is characterized by (BSMMU –Residency - MD/MS, Basic science, Paediatrics – March' 19)**

- a) variable expression of disorders
- b) early onset
- c) complete penetrance
- d) equal male-female involvement
- e) transmission only by females

Ans. a) T b) F(Late onset) c) F (Reduced penetrance) d) T e) F(equal male female transmission)]

**Q. Features of autosomal recessive disorders are (BSMMU – Residency - MD, MS, Basic Science, Dentistry - March '17)**

- a) not expressed in heterozygous state
- b) reduced penetrance
- c) onset usually in early life
- d) disease expression not uniform
- e) females are more affected

Ans. a) T b) F (complete penetrance) c) T d) F e) F (equally affected)

**Q. Features of autosomal dominant disorders (BSMMU – Non-Residency–MD, MS, Basic science – July' 16)**

- a) are expressed only in the homozygous states
- b) affects male more than the female
- c) follow Mendelian trait
- d) are expressed in receptors and structural proteins
- e) may transmitted to every generation

Ans. a) F b) F c) T d) T e) T

**Q. Characters of an autosomal dominant trait are (BSMMU – Residency – MD, MS, Basic – March' 15)**

- a) males are more affected than females
- b) most of the diseases are due to enzyme defect
- c) normal child is possible even if both of the parents are affected.
- d) the trait is seen in every generation
- e) new mutation is suspected if the parents are genetically normal

Ans. a) F b) F c) T d) T e) T

**Q. Given a husband with haemophilia and his unaffected wife (BSMMU – Residency - MD/MS, Basic science – March' 14)**

- a) none of their daughter will be affected
- b) all of their daughters will carry the haemophilic gene
- c) a daughter with Turner's syndrome may also have haemophilia
- d) all of his sisters will be carriers
- e) his maternal grandfather could have had haemophilia

Ans. a) T b) T c) T d) T e) T

**Q. Characteristics of autosomal dominant inheritants are (BSMMU – Non-Residency - MD – 13Ju)**

- a) two copies of the gene must be mutated for a person to be affected
- b) one mutated copy of the gene will be necessary for a person to be affected
- c) each affected person usually has one affected parent
- d) 25% child will inherit the mutated gene
- e) have reduced penetrance

Ans. a) F b) T c) T d) F e) T

**Q. Autosomal recessive diseases: (BSMMU - M. Phil, Diploma, July-'08)**

- a) are transmitted on 50% of offspring
- b) remains as carrier in 50% of offspring
- c) can be manifested even if one parent affected
- d) may be transmitted in offspring from apparently healthy parents
- e) are more common among female children.

F  
T  
T  
T  
F

**Q. Autosomal dominant inheritance is characterized by: (DMC – M. Phil, Diploma July, 08)**

- A. Transmission is usually vertical
- B. Parents are heterozygote
- C. Males are more affected than female
- D. Each offspring has a 25% chance of inheriting the abnormal gene
- E. New cases are due to gene mutation

T  
T  
F  
F  
T

**Q. In autosomal dominant inheritance: (DMC - MD/MS -06Ju)**

- a) males and females are equally affected
- b) a child of the affected parent has a 50% risk
- c) affected individuals present in every generation
- d) double dose of the mutant gene is required to manifest the disease
- e) normal offspring's may also transmit the condition

T  
T  
T  
F  
F

**Q. Autosomal dominant inheritance has the following characteristics:** (DMC - MD/MS -03Ja)

- |   |   |
|---|---|
| a) Affected patient usually has an affected parent. | T |
| b) Parents are heterozygous                         | T |
| c) Males are more affected than females             | F |
| d) Consanguinity is more common among parents       | F |
| e) Half of the offspring are affected.              | T |

**Q. An-X-linked recessive condition:** (DMC - MD/MS -02Ja)

- |   |   |
|---|---|
| A. Is manifest in females only when the gene is in the homozygous state     | T |
| B. Is transmitted by affected males and by female carrier                   | T |
| C. All daughters of an affected male are carriers                           | T |
| D. All sons of an affected male are affected                                | F |
| E. If a female carrier marries a normal male half her sons will be affected | T |

**Q. The following statements regarding autosomal dominant disorders:** (DMC – MD/MS -01Ja)

- |   |   |
|---|---|
| A. The disease manifests only in homozygous states.   | F |
| B. The diseases can not be manifested in heterozygous states.   | F |
| C. The disorders affect female more than males.   | F |
| D. Each offspring of a parent with autosomal dominant disorder has a 1 in 2 chance of inheriting the disease. | T |
| E. Genetic mutation can give rise to autosomal dominant disorders.  | T |

## Abnormalities Of Gene

**Q. Chromosomal abnormalities are found in** (BSMMU –Residency – MD, MS, Basic Science – March '15)

- a) Turner's syndrome
- b) Patau's syndrome
- c) mullerian agenesis
- d) Klinefelter's syndrome
- e) imperforate hymen

Ans. a) T b) T c) F d) T e) F

### HELP LINK:

Chromosomal and contiguous gene disorders:

A. Numerical chromosomal abnormalities:

Diseases	Locus	Clinical features
<b>Down's syndrome</b> (Trisomy 21)	47, XY, +21 or 47, XX, +21	Characteristic facies, IQ usually < 50, congenital heart disease, reduced life expectancy.
<b>Edward syndrome</b> (Trisomy 18)	47,XY, +18 or 47, XX, +18	Early lethality, characteristic skull and facies, frequent malformations of heart, kidney and other organs.
<b>Patau's syndrome</b> (Trisomy 13)	47, XY, +13 or, 47, XX, +13	Early lethality, cleft lip and palate, polydactyly, small head, frequent congenital heart disease
<b>Klinefelter's syndrome XXY</b>	47, XXY	Phenotypically male, Infertility, gynaecomastia, small testes
<b>XYY</b>	47, XYY	Usually asymptomatic, some impulse control problems
<b>Triple X syndrome</b>	47, XXX	Usually asymptomatic, may have reduced IQ
<b>Turner's syndrome</b>	45, X	Phenotypically female, short stature, webbed neck, coarctation of aorta, primary amenorrhoea

B. Recurrent deletions, microdeletions and contiguous gene defects:

- Di George/ velocardiofacial syndrome
- Prader-Willi syndrome
- Angelman's syndrome
- William's syndrome
- Smith-Magenis syndrome

(Ref: Davidson-23<sup>rd</sup>)

**Q. The following conditions occur due to abnormalities in autosome: (DMC - MD/MS -06Ja)**

- |                           |   |
|---------------------------|---|
| a. Down's syndrome        | T |
| b. Turner's syndrome      | F |
| c. Klinefelter's syndrome | F |
| d. Edward syndrome        | T |
| e. Patau's syndrome       | T |

**Q. Chromosome abnormality may occur in: (DMC – M. Phil, Diploma July, 2005)**

- |                                  |   |
|----------------------------------|---|
| a) klinifelter's syndrome        | T |
| b) treatment with antimicrobials | F |
| c) ionizing radiation            | T |
| d) Down's syndrome               | T |
| e) Christmas disease             | F |

#### DISEASES DUE TO CHROMOSOMAL MICRODELETIONS



Disease	Chromosome	Clinical features
DiGeorge syndrome	22	Facial dysmorphism, congenital heart disease (sometimes the only feature), absent parathyroids, palatal abnormalities
Williams' syndrome	7	Supravalvular aortic stenosis, facial dysmorphism, learning difficulties, hypercalcaemia
WAGR	11	Wilms tumour, aniridia, genitourinary abnormalities, mental retardation
Angelman's/Prader-Willi syndrome	15	Abnormal movements, ataxia, mental retardation, hypotonia, marked obesity

#### Classification of genetic disorders:

**A. Unifactorial disorders/ Single gene defects/ Mendelian disorders:** these disorders are due to defects of a single gene.

##### 1. *Autosomal disorders:*

- a. Autosomal dominant disorders: e.g. Achondroplasia
- b. Autosomal recessive disorders: e.g. Albinism

##### 2. *Sex-linked disorders:*

- a. X-linked dominant disorders: e.g. Familial hypophosphaetamic rickets.
- b. X-linked recessive disorders: e.g. Haemophilia

**B. Multi-factorial/ polygenic disorders:** Both environmental & genetic factors are responsible. The genetic component is complex. e.g.

- Ischaemic heart disease
- Essential hypertension
- Type 1 diabetes mellitus
- Congenital dislocation of hip.

**C. Chromosomal:** specific chromosomal abnormalities occur as:

##### 1. Numerical or alteration in number:

- a. Polyploidy
- b. Aneuploidy:
  - i. Autosomal e.g. Down's syndrome, Edward's syndrome, Patau syndrome
  - ii. Sex-chromosomal e.g. Turner's syndrome, Klinefelter's syndrome

##### 2. Structural: deletion, translocation, isochromosome, ring chromosome

##### 3. Combined.

(Ref: Davidson-23<sup>rd</sup>, Robbin's-9<sup>th</sup>)

**Q. Multifactorial disorders are (BSMMU – Non-Residency – MD, MS, Paediatrics, Basic Science – July' 19)**

- a) obesity
- b) hemochromatosis
- c) sickle cell anemia
- d) diabetes mellitus
- e) Turner's syndrome

Ans. a) F b) F c) F d) T e) F

(Ref: Emery elements of medical Genetics-14<sup>th</sup>, P-144)

**Q. Mendelian disorders involve- (BSMMU-MS-04Ja)**

- |                       |   |
|-----------------------|---|
| a) Single gene        | T |
| b) Multiple genes     | F |
| c) Mitochondrial gene | F |
| d) Autosome           | T |
| e) Sex chromosome     | T |

**Q. The following genetic disorders are associated with congenital heart disease: (BSMMU - M. Phil, Diploma, July-08)**

- |                           |   |
|---------------------------|---|
| a) klinefelter's syndrome | F |
| b) trisomy 18             | T |
| c) turners syndrome       | T |
| d) super female           | F |
| e) down's syndrome        | T |

**Q. The following conditions occur due to abnormalities in autosome: (DMC – M. Phil, Diploma July, 2006)**

- |                           |   |
|---------------------------|---|
| a) Down's syndrome        | T |
| b) Turner's syndrome      | F |
| c) Klinefelter's syndrome | F |
| d) Edward's syndrome      | T |
| e) Patau's syndrome       | T |

**Mutation**

**Q. Following are the example of point mutations: (BSMMU – M. Phil, Diploma, July-09)**

- |                          |   |
|--------------------------|---|
| a) achondroplasia.       | T |
| b) myotonic dystrophy    | F |
| c) haemochromatosis      | T |
| d) ataxia telangiectasia | F |
| e) fragile X syndrome    | F |

**HELP LINK:**

A mutation may be defined as permanent change in the DNA.

**Types:**

- A. **Genome mutation** – Loss or gain of whole chromosome
- B. **Chromosome mutation** – Involving number or structure.
- C. **Gene mutation** – results in partial or complete deletion of a gene.

It is of 2 types-

- a) **Frame-shift mutation:** This type of mutation occurs when one nucleotide base added or deleted from a DNA molecule, resulting in total alteration of a frame of a gene.
- b) **Point mutation:** When there is insertion of one nucleotide base instead of another. Here alteration of only one gene occurs and all other gene sequence of a DNA is normal. Again it is of 3 types –
  - 1) **Missense mutations:** In a missense mutation, the new base alters a codon resulting in a different amino acid being incorporated into the protein chain.
  - 2) **Nonsense mutations:** In a nonsense mutation, the new base changes a codon that specified an amino acid into one of the stop codons.
  - 3) **Silent mutations:** Silent mutations are those that cause no change in the final protein product and can only be detected by sequencing the gene.

(Ref: Robbins-8<sup>th</sup>, P-138, 139; Lippincott's Biochemistry)

**Causes of mutation:**

1. Spontaneous mutation
2. Mutagens:
  - Physical mutation: UV rays, Ionizing radiation
  - Chemical mutations: Anti-cancer drugs
  - Viruses: rubella viruses.

(Ref: Robins pathology)

**KARYOTYPING**

Karyotyping is done in

1. **Cytogenetic disorders involving autosomes:**
  - Down's syndrome/ Trisomy 21: 47,XX + 21
  - Edward's syndrome/ Trisomy 18: 47,XX + 18
  - Patau's syndrome/ Trisomy 13: 47, XX + 13
2. **Cytogenetic disorders involving sex chromosomes:**
  - Klinefelter's syndrome: 47,XXY
  - Turner's syndrome: 45,XO

**3. Single gene disorder:**

- Trinucleotide repeat disorder- Fragile X syndrome
- Prader willi syndrome
- Angelman syndrome

**Question Bank****Q. Increase in the number of chromosomes occur in (BSMMU –Residency - Basic science – March' 19)**

- a) Turner syndrome
- b) Fragile X-syndrome
- c) Down syndrome
- d) Klinefelter's syndrome
- e) retinoblastoma

Ans.

- a) F(45X0)
- b) F (genetic disorder occurs as a mutation of the *fragile X mental retardation 1 (FMR1)* gene on the X chromosome)
- c) T (Trisomy 21)
- d) T (47XXY)
- e) F (AD syndrome, 40% familial, 60% sporadic, Osteosarcoma associated with retinoblastoma)

**Q. Cytogenetic disorders involving sex chromosomes are (BSMMU –Residency – MD, MS, Basic Science – March' 18)**

- a) Turner syndrome
- b) Klinefelter syndrome
- c) Down syndrome
- d) Edward syndrome
- e) Hermaphroditism

Ans. a) T b) T c) F d) F e) T

**Q. Examples of trisomy are (BSMMU – Residency - MD, MS, Basic Science - March' 17)**

- a) Turner's syndrome
- b) Down's syndrome
- c) Edward's syndrome
- d) Klinefelter's syndrome
- e) Marfan's syndrome

Ans. a) F b) T c) T d) T e) F

**Help link:** Sex chromosomal trisomy are Klinefelter syndrome, Triple X syndrome, 47XYY.

**Q. Karyotypes indicate sex chromosomal aneuploidy are (BSMMU – Residency – MD, MS, Basic science – March' 16)**

- |                   |                          |
|-------------------|--------------------------|
| a) 47, XXX        | T                        |
| b) 47, XXY        | T                        |
| c) 47, XY+21      | F (Autosomal aneuploidy) |
| d) 47, X0         | F                        |
| e) 46, XX/ 46, XY | F                        |

**Q. A Karyotype gives an idea about: (BSMMU – M. Phil, Diploma July, 2006)**

- |  |   |
|--|---|
| a) Number of chromosome                                    | T |
| b) Type of chromosome on the basis of centromeric position | T |
| c) Structural basis of chromosome                          | T |
| d) Sex of the individual                                   | T |
| e) Functional status of the chromosome                     | T |

**Q. Karyotyping is indicated in the following conditions: (BSMMU-06Ja)**

- A. suspected Down's syndrome
- B. recurrent pregnancy loss
- C. primary amenorrhoea
- D. meningo- myelocele
- E. Fallot's tetralogy

Ans.

- a) T (*Karyotype - 47 XY+21*)
- b) T
- c) T (*Turner's syndrome is the single most common cause of primary amenorrhoea, about one third of the cases*)
- d) F
- e) T (*Down's syndrome is associated with TOF*)

**Q. Karyotyping is indicated in: (BSMMU – M. Phil, Diploma July, 2005)**

- |                        |   |
|------------------------|---|
| a) Edward's syndrome   | T |
| b) Down's syndrome     | T |
| c) meningomyelocele    | F |
| d) ambiguous genitalia | F |
| e) phenylketonuria     | F |

**Q. Karyotyping may help in diagnosis of: (DMC - MD/MS -05Ja)**

- |                                |   |
|--------------------------------|---|
| a) Cystic fibrosis             | F |
| b) Down's syndrome             | T |
| c) Klinefelter's syndrome      | T |
| d) Haemophilia                 | F |
| e) Duchenne muscular dystrophy | F |

**Q. Karyotypes found in different conditions - (BIRDEM-04)**

- |   |                        |
|---|------------------------|
| a) 46, XY in Testicular feminization    | T                      |
| b) 47, XXX in super female              | T                      |
| c) 47, XYY in Klinefelter's syndrome    | F                      |
| d) 45, OX in Mongolism                  | F                      |
| e) 47, trisomy 21 in Turner's syndrome. | F (in Down's syndrome) |

**Q. The karyotype - (DMC - MD/MS -03Ja)**

- a) Of a normal male is 46xy
- b) Of a female with down syndrome is 47 xx, +21
- c) Of a male with cri-du-chat syndrome is 45xy 5p
- d) In turner is syndrome is 46x
- e) 47xxy is compatible with health and behavior

**Ans.**

- a) T b) T  
 c) F (deletion of the short arm of chromosome 5)  
 d) F  
 eT (supermale, usually asymptomatic & tall)

**Q. The following karyotypes indicate Down's syndrome- (BSMMU - M.Phil/ Diploma - 01Ju)**

a) 47 XY, +21	T
b) 47 XXY	F
c) 47 XX +21	T
d) 47 XX +21/ 46 XX	T
e) 47 XX, +21/ 47 XY, +21	F

**Q. Karyotype association- (BSMMU-MS-01Ja)**

a) Down's syndrome: 47, XX + 18	F
b) Patau's syndrome: 47, XX + 13	T
c) Klinefelter's syndrome: 45, X	F
d) Turner's syndrome: 47, XX + 21	F
e) Edward's syndrome: 47, XYY	F

**Q. Trisomy 21 on karyotyping indicates- (BSMMU - MD - 02Ja)**

a) Edward syndrome	F
b) Patau's syndrome	F
c) Down syndrome	T
d) Rotor syndrome	F
e) Dubin-Jhonson syndrome	F

## Prenatal testing

**Q. Prenatal chromosome analysis can be done from (BSMMU-Residency-MD,MS, Basic Science- March' 17)**

- a) amniotic fluid  
 b) chorionic villous tissue  
 c) foetal cord blood  
 d) maternal peripheral blood  
 e) maternal skin fibroblasts

**Ans. a) T b) T c) T d) F e) F**

**Help link:** Double, Triple and Quadraple tests are done for Down's syndrome in 2<sup>nd</sup> trimester, nuchal translucency by USG detected in 1<sup>st</sup> trimester.

**Q. Followings are the screening tests for fetal chromosomal anomalies (BSMMU – Non-Residency – MS, Basic science – July' 14)**

- a) amniocentesis  
 b) chorionic villus sampling  
 c) triple test  
 d) double test  
 e) nuchal translucency

**Ans. a) T b) T c) F d) F e) F****Help link:****Methods used in prenatal testing:**

Test	Gestation	Comments
Ultrasound	1 <sup>st</sup> trimester onwards	Increased nuchal translucency (an oedematous flap of skin at the base of the neck) for trisomies and Turners; all major abnormalities such as neural tube defects (NTDs), congenital heart disease

<b>Chorionic villus biopsy</b>	From 11 weeks	2% risk of miscarriage; used for early chromosomal, DNA and biochemical analysis; a specialised test
<b>Amniocentesis</b>	From 14 weeks	<1% risk of miscarriage; used for chromosomal and some biochemical analysis, e.g. $\alpha$ -fetoprotein for NTD
<b>Cordocentesis</b>	From 19 weeks	2-3% risk of miscarriage; a highly specialised test; used for chromosomal and DNA analysis

(Ref: Davidson-23<sup>rd</sup>)

## KLINEFELTER'S SYNDROME

**Q. A person with karyotype 47 XXY is associated with:** (BSMMU – M. Phil, Diploma (Non-Residency)– March-2012, DMC & others – MS – March-2012)

- a) mongolism F
- b) a single barr body T
- c) presence of an ovotestis F
- d) gynaecomastia T
- e) mental retardation T

**HELP LINK:**

**KLINEFELTER'S SYNDROME:**

K = Karyotype is 47, XXY (classical).

L = Leydig cell dysfunction resulting in hypogonadism.

I = Increased risk of breast cancer in later

N = (Results from) Nondisjunction during the meiotic divisions in one of the parents.

E = Enlarged breast (gynaecomastia).

F = Firm & small testes.

E = Epiphyseal closure delayed.

L = Long leg length associated with 47XXY.

T = Tall stature is apparent from early childhood.

E = Evident from infancy and possibly even in utero & gradually progresses with age

R = Reduced plasma testosterone level.

S = Seminiferous tubules dysgenesis, reduced spermatogenesis, male infertility.

S = Small & atrophied testes.

Y = Y chromosome is one or more; two or more X-chromosome.

N = Normal to borderline IQ, learning difficulties.

D = Diabetes mellitus (Type-2), Delayed Emotional maturity,

R = Raised serum FSH (Hypergonadotropic hypogonadism).

O = Occasional mental retardation (in 10% cases).

M = Maternal age ( $\uparrow$  maternal age  $\rightarrow$   $\uparrow$  KS).

E = Eunuchoid body habitus with abnormally long legs.

**Q. Followings are the features of Klinefelter's syndrome:** (BSMMU – M.Phil, Diploma-July,10)

- a) Most common karyotype is 47 XXX F
- b) Phenotype is male T
- c) usually have short stature F
- d) All have gynaecomastia F
- e) Usually are infertile T

**HELP LINK:**

■ **Klinefelter syndrome:** It is a chromosomal abnormality in which the cells have 47 chromosomes with a sex chromosomal pattern of XXY. It is due to nondisjunction of XX homologous chromosome in most of the cases.

■ **Karyotype:** 47XXY

**C/F:**

1. Tall stature
2. Obese.
3. Gynaecomastia (Ca of breast may develop in 20% cases)
4. Small phallus, cryptorchidism. Hypospadias in some.
5. Absence of secondary sex characters (axillary, pubic hair, beard)
6. High pitched voice
7. Eunuchoid long lower limb.
8. Behavioural & psychiatric disorder, anti-social, immature, aggressive.

**Inv:**

1. Serum testosterone (usually low)
2. Gonadotrophic hormones (increased FSH & LH)
3. Serum oestrogen ( $\uparrow$ )
4. Azoospermia is universal.
5. Chromosomal analysis (2 or more X-chromosome, one or more Y chromosome)

**Rx:**

1. No specific Rx
2. Androgen (testosterone)
3. Plastic surgery for gynaecomastia
4. Life span is usually normal.

(Ref: Davidson-23<sup>rd</sup>)**Q. The number of chromosome in a cell of a person in Klinefelter's syndrome are:** (DMC - MD/MS -04Ja)

- a) 45              F  
 b) 47              T  
 c) 44              F  
 d) 48              F  
 e) 46              F

**TURNER'S SYNDROME****Q. Karyotypes that indicate Turner syndrome are** (BSMMU –Residency - MD/MS, Basic science, Paediatrics – March '19)

- a) 47, XXX  
 b) 45,X<sup>-</sup>  
 c) 46,X,del (Xq)  
 d) 47,XXY  
 e) 46,XY

Ans. a) F b) T c) T d) F e) F

**Q. Turner's syndrome is characterized by** (BSMMU – Non-Residency – MS, Basic science – July' 18)

- a) 45 XY chromosomal abnormality  
 b) secondary amenorrhoea  
 c) coarctation of the aorta  
 d) multicystic ovary  
 e) absence of pubic hair

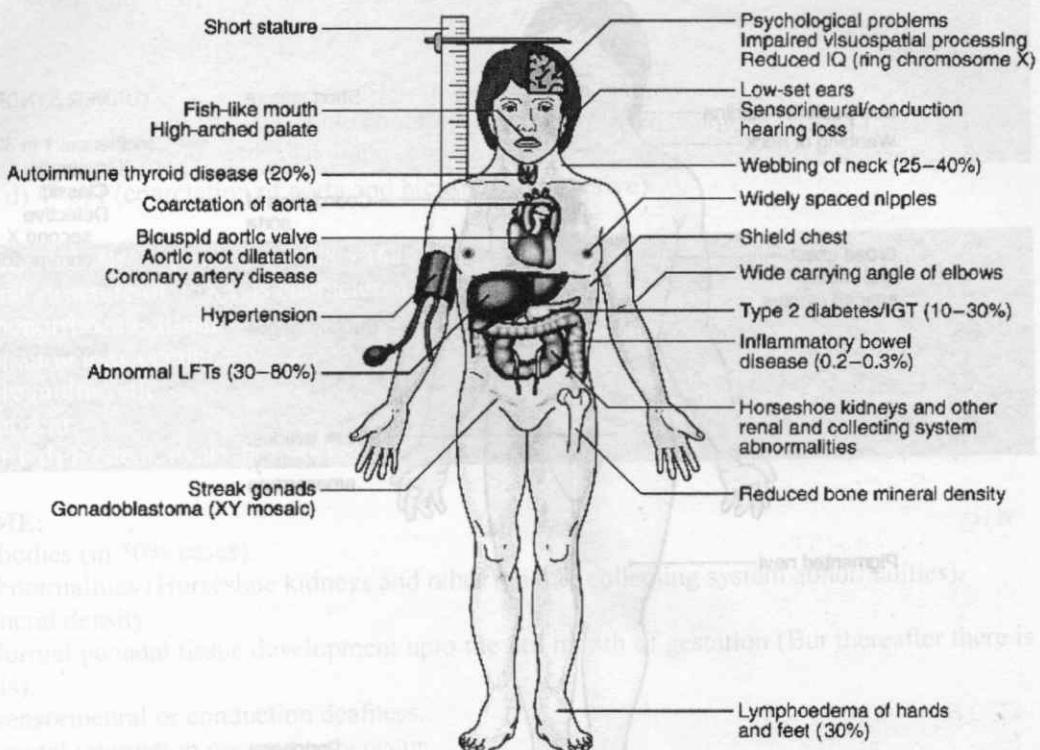
Ans. a) F b) F c) T d) F e) F

**Help link:**

**■ Definition:** It is a sex chromosomal abnormality characterized by the cells have 45 chromosomes with an XO chromosomal complement caused by nondisjunction in male gamete during meiosis.

Turner's syndrome affects approximately 1 in 2500 females.

**Fig: Clinical features of Turner's syndrome (45XO). (IGT = impaired glucose tolerance)**



The syndrome is classically associated with a 45XO karyotype, but other cytogenetic abnormalities may be responsible, including mosaic forms (e.g. 45XO/46XX or 45XO/46XY) and partial deletions of an X chromosome.

#### Clinical features:

Individuals with Turner's syndrome invariably have short stature from an early age and this is often the initial presenting symptom. It is probably due to the absence of one copy of a *SHOX* gene, located on chromosome X and Y, which codes a protein that is predominantly found in bone fibroblasts.

The genital tract and external genitalia in Turner's syndrome are female in character, since this is the default developmental outcome in the absence of testes. Ovarian tissue develops normally until the third month of gestation, but thereafter there is gonadal dysgenesis with accelerated degeneration of oocytes and increased ovarian stromal fibrosis, resulting in 'streak ovaries'. The inability of the ovarian tissue to produce oestrogen results in loss of negative feedback and elevation of FSH and LH concentrations.

There is a wide variation in the spectrum of associated somatic abnormalities. The severity of the phenotype is, in part, related to the underlying cytogenetic abnormality. Mosaic individuals may have only mild short stature and may enter puberty spontaneously before developing gonadal failure.

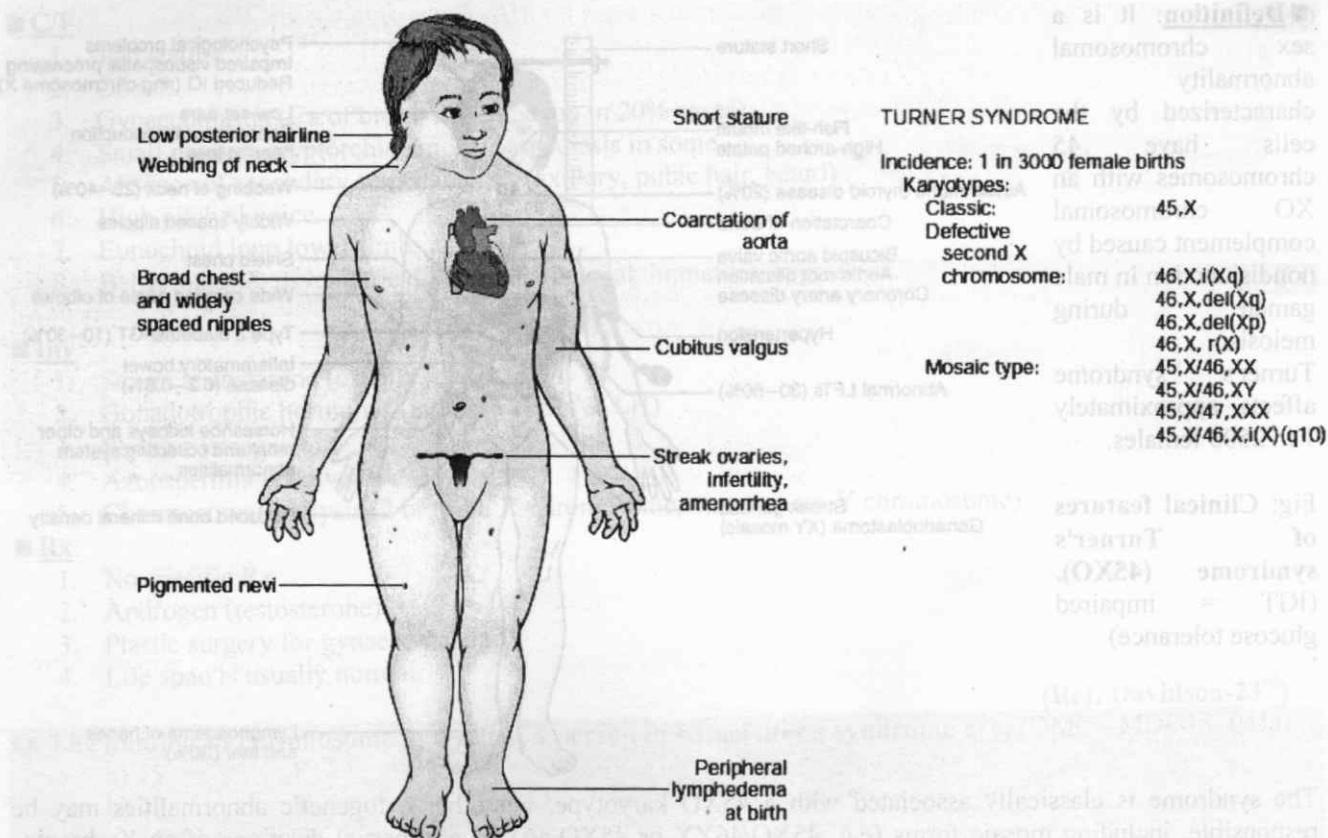


Figure 5-22 Clinical features and karyotypes of Turner syndrome.

**Diagnosis and management:** The diagnosis of Turner's syndrome is confirmed by karyotype analysis. Short stature, although not directly due to growth hormone deficiency, responds to high doses of growth hormone. Prophylactic gonadectomy is recommended for individuals with 45XO/45XY mosaicism because there is an increased risk of gonadoblastoma. Pubertal development is induced with oestrogen therapy, but will result in fusion of the epiphyses and cessation of growth. Therefore, the timing of pubertal induction needs to be carefully planned. Adults with Turner's syndrome require long-term oestrogen replacement therapy and should be monitored periodically for the development of aortic root dilatation and other somatic complications.

(Ref: Davidson-23<sup>rd</sup>)

■ **C/F:**

1. Short stature
2. Neck- short, webbing, low hairline on the back of neck.
3. Face- small lower jaw (micrognathia); mouth is small & fish like, high arched palate, low set ears.
4. Chest- broad, widely apart nipples (shield-like chest)
5. Hand- short 4<sup>th</sup> metacarpals, lymphoedema of hands (also foot), nails- absent/- dysplastic
6. Elbow- increased carrying angles (cubitus valgus)

■ **Inv:**

1. Karyotyping from buccal smear- 45 (XO) is classical, occasionally 46 (XX) mosaics.
2. USG (small uterus, fallopian tube, streak gonad)
3. Hormone assay (low oestrogen, high LH & FSH)

■ **Rx:**

1. Oestrogen therapy at puberty.
2. Growth hormone
3. Gonadal tumour if occur- remove.

**Q. Feature/s of Turner's syndrome is/are (BSMMU – Residency – MD, Basic Science – March '18)**

- a) low hairline
- b) pitting edema
- c) shield chest
- d) webbed neck
- e) ventricular septal defect

Ans. a) T b) T c) T d) T e) F (coarctation of aorta and bicuspid aortic valve)

**Q. In Turner's syndrome: (BSMMU – Residency – MS – March '13)**

- a) A chromosomal structure of 45XY is characteristic
- b) Secondary amenorrhoea is usual
- c) Coarctation of aorta may occur
- d) The ovaries are multicystic
- e) Pubic hair is absent

Ans. a) F b) F c) T d) F (steak ovary present) e) F

**Help link:****TURNERS SYNDROME:**

T = Thyroid auto-antibodies (in 50% cases).

U = Urinary system abnormalities (Horseshoe kidneys and other renal & collecting system abnormalities).

R = Reduced bone mineral density.

N = Neck webbing, Normal gonadal tissue development upto the 3rd month of gestation (But thereafter there is gonadal dysgenesis).

E = Ears are low set, sensorineural or conduction deafness.

R = Reduced IQ but mental retardation uncommonly occur.

S = Streak gonads, infertility, primary amenorrhoea, gonadoblastoma.

S = Shield chest, Short stature.

Y = Y chromosome is usually absent (classical karyotype is 45X0).

N = Nipples are widely spaced.

D = Diabetes mellitus (type-2), IGT.

R = Raised blood pressure, coarctation of aorta, aortic root dilatation, coronary artery disease.

O = Oestrogen therapy is the mainstay of treatment.

M = Menopause occurs before menarche.

E = Estrogen deficiency but elevated FSH & LH concentrations.

**Q. Characteristics of classic turner's syndrome are: (BSMMU – M. Phil, Diploma (Non-Residency)–March-2012, DMC & others – MS – March-2012)**

- |                                 |   |
|---------------------------------|---|
| a) a chromosome number of 45 XY | F |
| b) secondary amenorrhoea        | F |
| c) coarctation of the aorta     | T |
| d) multicystic ovaries          | F |
| e) absence of pubic hair        | F |

**Q. Turner syndrome is associated with: (BSMMU – M. Phil, Diploma – 11Ju, DMC & others – MD – 11Ju)**

- |                               |   |
|-------------------------------|---|
| a) primary amenorrhoea        | T |
| b) 45X0 karyotype             | T |
| c) rare mental retardation    | T |
| d) autosomal dominant disease | F |
| e) male phenotype.            | F |

**Q. In Turner's syndrome: (BSMMU –MS-January, 2009)**

- a) a chromosome structure of 45XY is characteristics F
- b) Secondary amenorrhoea F
- c) Coarctation of the aorta may occur T
- d) Ovaries are multicystic F
- e) Pubic hair is absent F

**Q. In Turner's syndrome: (BSMMU – MS -08Ja)**

- a) The patient usually has primary amenorrhoea T
- b) The karyotype is 45XO T
- c) The patient is usually tall F
- d) There is poor breast development T
- e) mental retardation is common F

**Q. Turner's syndrome: (BSMMU – MD – January, 2010)**

- a) is a common cause of male hypogonadism F
- b) results from complete? partial monosomy of X chromosome T
- c) is characterized by 47XXY karyotype in most cases F
- d) is an important cause of primary amenorrhoea T
- e) is a cytogenetic disorder involving autosome F

**Q. Characteristic features of Turner's syndrome include: (DMC – M. Phil, Diploma July, 2007)**

- a) primaty amenorrhoea T
- b) tall stature F
- c) webbing of neck T
- d) cubitus valgus T
- e) coarctation of aorta T

**Q. Characteristic feature of turner's syndrome include: (M. phil, Diploma – 03Ju)**

- a. Primary amenorrhoea T
- b. Tall stature F
- c. Webbing of the neck T
- d. Cubitus valgus T
- e. Aortic coarctation T

**Q. The followings are associated will Turner's syndrome— (BSMMU-M.Phil, Diploma -Sur-02Ju)**

- a) Gynaecoid pelvis T
- b) Coarctation of the aorta T
- c) Short fourth metacarpal T
- d) Flattening the medial tibial condyle F
- e) Arachnodactyly. F

**Q. Turner's syndrome is characterized by - (BSMMU - M.Phil/ Diploma - 00Ju)**

- a) 45 XO T
- b) 47 XXY F
- c) Short stature T
- d) Webbing of neck T
- e) Flat facial profile F

## Down's syndrome

**Q. Down's syndrome may be associated with (BSMMU – Non-Residency – MD, Basic Science – July' 17)**

- a) Endocardial cushion anomaly
- b) bronchiectasis
- c) congenital duodenal atresia
- d) systemic hypertension
- e) hypothyroidism

Ans. a) T b) F c) T d) F e) T

### HELP LINK:

It is the most common of the chromosomal disorders and a leading cause of mental retardation.

**Incidence:** 1 in 700 live births, the incidence increases sharply with advancing maternal age ( $>35$  years)

**Genetic defect:**  $> 95\%$  of the affected individuals have trisomies for chromosome 21 and the remainder translocations.

<b>Clinical features:</b>	
<b>General</b>	<ul style="list-style-type: none"> <li>• Mental retardation (IQ &lt;50)</li> <li>• Short stature</li> <li>• Hypotonia</li> <li>• Quite affectionate temperament</li> <li>• Reduce life expectancy in 40%</li> <li>• Increased risk to leukaemia</li> </ul>
<b>Head, Neck &amp; Face</b>	<ul style="list-style-type: none"> <li>• Oblique palpebral fissure</li> <li>• Marked epicanthic fold</li> <li>• Flat facial profile</li> <li>• Flat nasal bridge</li> <li>• Low set ears</li> <li>• Abundant neck skin</li> </ul>
<b>Thorax and abdomen</b>	<ul style="list-style-type: none"> <li>• Congenital Heart defect eg. VSD, ASO, PDA, TOF etc.</li> <li>• Duodenal atresia</li> <li>• Intestinal hernia</li> <li>• Imperforate anus</li> <li>• Umbilical hernia</li> </ul>
<b>Hand and feet</b>	<ul style="list-style-type: none"> <li>• Short and broad hand</li> <li>• Single palmar (simian) crease</li> <li>• Wide gap between 1st and 2nd toes</li> </ul>

### Investigations:

#### Karyotyping -

- a) Trisomy 21: 47, XX + 21 or 47, XY + 21 (95%)
- b) Translocation type (Robertsonian): (4%) 46,XX, der (14, 21) (q10, q10) + 21
- c) Mosaic type (1%): 46,XX/ 47 XX + 21

### Treatment:

1. Advice to parents

2. Genetic counseling-

- a) Antenatal diagnosis by amnio-centesis (15-16Wks) and chorionic villous sampling (9 -11Wks)
- b) Detection of carrier is possible by chromosome analysis, DNA-analysis technology

(Ref: Basic MRCP + Davidson's Medicine + Robbins)

**Q. A Down syndrome baby may have (BSMMU – Non-Residency – MD, Basic science – 13Ju)**

- |                                     |   |
|-------------------------------------|---|
| a) ventricular septal defect        | T |
| b) hypertonia of limbs              | F |
| c) gastrointestinal tract anomalies | T |
| d) hyperthyroidism                  | F |
| e) splenomegaly                     | F |

**Q. Down's syndrome is:** (BSMMU – Residency – MD – March'13)

- a) X-linked recessive disorder
- b) Associated with increased maternal age
- c) A trisomy 21 disorder
- d) Associated with coarctation of aorta
- e) Diagnosed by Barr body analysis

Ans : a) F b) T c) T d) F e) F

**Q. Down syndrome:** (BSMMU – M. Phil, Diploma (Non-Residency)–March-2012, DMC & others – MD/MS – March-2012)

- a) in 25% of cases are due to mosaicism
- b) can be screened out by Barr body examination
- c) is more accurately diagnosed by amniocentesis than by hormonal tests
- d) is associated with the age of the mother
- e) is a Mendelian disorder

Ans. a) F (1% cases) b) F c) T ( $\alpha$  fetoprotein and  $\beta$  HCG estimation in 2<sup>nd</sup> trimester)  
d) T (Important cause of non-dysjunction) e) F

**Q. Features of Down's syndrome include:** (BSMMU – MD – January, 2010)

- |  |  |
|--|--|
| a) trisomy of chromosome 21                    | T  |
| b) normal parental karyotype                   | T  |
| c) more affected females than males            | T  |
| d) increased risk for developing Wilm's tumour | F  |
| e) mental retardation                          | T (Number one cause of mental retardation) |

**Q. A Down's syndrome baby may have:** (BSMMU – MD - January, 2009)

- |                                  |   |
|----------------------------------|---|
| a) Ventricular septal defect     | T |
| b) Hypothyroidism                | T |
| c) Congenital GI tract anomalies | T |
| d) Splenomegaly                  | F |
| e) Hypertonia in the limbs       | F |

**Q. The followings are associated with Down's Syndrome-** (BSMMU-MS-07Ja)

- |                             |   |
|-----------------------------|---|
| a) Trisomy of chromosome-21 | T |
| b) Duodenal atresia         | T |
| c) Rectal polyp             | F |
| d) Atrial septal defect     | T |
| e) Umbilical hernia         | T |

**Q. Genetic abnormality in a Down syndrome child be-** (BSMMU-MS-02Ja)

- |                                     |   |
|-------------------------------------|---|
| a) Fragile sites in 'X' chromosome  | F |
| b) Mosaicism                        | T |
| c) Triploid                         | F |
| d) An extra chromosome 21           | T |
| e) Point mutation in chromosome 21. | F |

**Q. Down's syndrome-** (BSMMU-Sur-02/01Ja)

- |   |   |
|---|---|
| a) Is a cytogenetic disorder involving autosom        | T |
| b) Is strongly influenced by maternal age             | T |
| c) Has an iliac index over 78.                        | F |
| d) May have eleven pairs of ribs                      | F |
| e) May be associated with duodenal atresia & stenosis | T |

**Q. Trisomy 21 on karyotyping indicates- (BSMMU-02Ja)**

- |                           |   |
|---------------------------|---|
| a) Edward syndrome        | F |
| b) Patan's syndrome       | F |
| c) Down syndrome          | T |
| d) Rotor syndrome         | F |
| e) Dubin-Jhonson syndrome | F |

**Q. In Down syndrome - (BSMMU - M.Phil/ Diploma - 00Ju)**

- |   |                |
|---|----------------|
| a) Over 90% of the affected individual have trisomy 21. | T              |
| b) Most common cause is mitotic nondisjunction          | T              |
| c) Paternal age has a strong influence                  | F (mother age) |
| d) Hypothyroidism occurs in 1% of cases                 | T              |
| e) Hypotonia is generally present.                      | T              |

**Indication of chromosome analysis**

- cong. malformation
- Mental retardation
- Repeated abortion
- Sex determination
- Prenatal diagnosis

**Karyotype**

- Chromosomal constitution of an individual
- Photograph of an individual chromosomes arranged in standard manner
- Helps proper identification and numbering of chromosomes, numerical and structural abnormalities of chromosomes.
- What type of cell chosen for it: rapidly dividing cells, lymphocytes(mostly), fibroblasts from skin, bone marrow cells, chorionic villi, amniotic fluid cells,

**Sex chromatin/ bar body**

- Female interphase nucleus shows a dark stained chromatin mass attached on one side of the nuclear membrane.
- Samples collected: buccal mucosa(mostly), skin, vaginal or urethral epithelium, blood cell.
- Nucleus of female polymorphs show a drumstick, absent in male
- Inactive of the X chromosome(process of inactivation of X chromosome is called Lyon hypothesis).
- Karyotype determines sex accurately.
- Normal male: no barr body
- Normal female: one barr body
- Turner syndrome(XO): no barr body
- Kline felter syndrome(XXY): one barr body
- Triple X syndrome: two barr body.
- ❖ History of human population can be traced through the study of Y chromosome.

**Mitochondrial disorder**

- Mitochondrial DNA is maternally inherited.
- Mitochondria present only in maternal oocyte, therefore called cytoplasmic inheritance.
- Affected male cannot transmitted the disease
- Human cells has many thousands of mitochondria.
- Mitochondrial DNA show high mutation rate.
- C/F: hypotonia of skeletal muscle, cardiomyopathy, neuropathy, seizures, dementia, encephalopathy, ataxia, stroke, dystonia, acidosis

**Table 1.9 More common mitochondrially inherited disorders**

Disorder	Features
MELAS	Mitochondrial Encephalopathy, Lactic Acidosis, Stroke-like episodes, diabetes mellitus
MERRF	Myoclonic Epilepsy, Ragged-Red Fibres in muscle, ataxia, sensorineural deafness
NARP	Neuropathy, Ataxia, Retinitis Pigmentosa, developmental delay, lactic acidosis
Chronic progressive external ophthalmoplegia	Ptosis, ophthalmoplegia
Leber's hereditary optic neuropathy	Visual loss, neurodegenerative features
Hypertrophic cardiomyopathy with myopathy	HOCM, muscle weakness
Diabetes with deafness	Diabetes mellitus, sensorineural deafness
Aminoglycoside-induced deafness	Deafness induced by use of aminoglycoside antibiotics
Pearson syndrome	Pancreatic insufficiency, pancytopenia, lactic acidosis

**Multifactorial or polygenic inheritance:****Mendelian**

Gene results in disease

All or nothing

Risk does not increase through life

**Multifactorial**

May have many contributing genes, do not develop disease if less than threshold

Additive with a varying phenomenon

May acquire increasing liability through life

**Example:****1. Cong. Malformation:**

- a. Neural tube defects
- b. spina bifida,
- c. anencephaly
- d. Cong heart disease
- e. Cleft lip and cleft palate
- f. Pyloric stenosis
- g. Cong. Dislocation of hip
- h. Hirschprung disease

**2. Common adult disease**

- a. IDDM
- b. Schizophrenia
- c. Manic depression
- d. Breast cancer
- e. RA
- f. Epilepsy
- g. Multiple sclerosis
- h. PUD
- i. Glaucoma
- j. Essential HTN
- k. IHD
- l. Asthma
- m. Alzheimer disease

**Conditions for which gene therapy has been attempted**

- 1. Adenosine deaminase immune deficiency
- 2. Thalassaemia
- 3. Sickle cell disease
- 4. Phenylketonuria.
- 5. Haemophilia A
- 6. Cystic fibrosis
- 7. Duchenne muscular dystrophy.

**PCR**

- Modern diagnostic procedure, allowing amplification of target DNA sequences through repeated cycles of DNA with the help of DNA polymerase enzyme.
- Components:
  - Template DNA
  - Oligonucleotide primers
  - DNA polymerases
  - Deoxynucleotide triphosphatase.
- Sample may be: blood, tissue, saliva, semen, bone, nail, hair.

**Application to medicine**

1. Diagnosis of infections, e.g. mycobacteria, HIV, meningococcus, herpes simplex.
2. Forensics (hair, blood, semen).
3. Quantification of gene expression (where mRNA template is first reverse transcribed into a cDNA equivalent before amplification (RT-PCR)).
4. Prenatal diagnosis from chorionic villus sampling, of known genetic mutations, e.g. cystic fibrosis, Duchenne muscular dystrophy.
5. Detection of minimal residual tumour (e.g. *bcr-abl* in chronic myeloid leukaemia) and mutations in malignant tumours to assess prognosis.
6. Investigation of evolution of pathogens, e.g. HIV, SIV.
7. Tissue typing by PCR and detection of other variants, especially of MHC (major histocompatibility complex) class II.

## Single-Gene Disorders with Nonclassic Inheritance

It has become increasingly evident that transmission of certain single-gene disorders does not follow classic Mendelian principles. This group of disorders can be classified into four categories:

- Diseases caused by trinucleotide-repeat mutations
- Disorders caused by mutations in mitochondrial genes
- Disorders associated with genomic imprinting
- Disorders associated with gonadal mosaicism

**Q. Examples of trinucleotide repeat expansion disease include (BSMMU – Non-Residency – MD/MS, Basic science – July' 14)**

- a) fragile X syndrome
- b) cystic fibrosis
- c) Duchenne muscular dystrophy
- d) myotonic dystrophy
- e) Friedreich's ataxia

Ans. a) T b) F c) F d) T e) T

**Help link:**

### Trinucleotide-repeat mutations

- Amplification of sequence of three nucleotides
- They are dynamic (the degree of amplification increases during gametogenesis).
- almost all affected sequences share the nucleotides guanine (G) and cytosine (C).
- Eg: fragile X syndrome  
 there are 250 to 4000 tandem repeats of the sequence CGG within a gene called *familial mental retardation 1 (FMR1)*.
- DNA is unstable
- Expansion of the repeats above a certain threshold impairs gene function in various ways

- diseases associated with unstable tetra-, penta-, and hexa- nucleotides have also been found establishing this as a fundamental mechanism of neuromuscular diseases.
- Mechanisms:
  - (1) *Loss of function of the affected gene*, typically by transcription silencing, as in fragile X syndrome. In such cases the repeats are generally in non-coding part of the gene
  - (2) *A toxic gain of function* by alterations of protein structure as in Huntington disease and spinocerebellar ataxias. In such cases the expansions occur in the coding regions of the genes.
  - (3) *A toxic gain of function mediated by mRNA as is seen in fragile X tremor-ataxia syndrome.* As in fragile X syndrome, the noncoding parts of the gene are affected

**Table 5-8 Examples of Trinucleotide-Repeat Disorders**

Disease	Gene	Locus	Protein
<b>Expansions Affecting Noncoding Regions</b>			
Fragile X syndrome	<i>FMR1 (FRAXA)</i>	Xq27.3	FMR-1 protein (FMRP)
Friedreich ataxia	<i>FXN</i>	9q21.1	Frataxin
Myotonic dystrophy	<i>DMPK</i>	19q13.3	Myotonic dystrophy protein kinase (DMPK)
<b>Expansions Affecting Coding Regions</b>			
Spinobulbar muscular atrophy (Kennedy disease)	<i>AR</i>	Xq12	Androgen receptor (AR)
Huntington disease	<i>HTT</i>	4p16.3	Huntingtin
Dentatorubral-pallidoluysian atrophy (Haw River syndrome)	<i>ATNL</i>	12p13.31	Atrophin-1
Spinocerebellar ataxia type 1	<i>ATXN1</i>	6p23	Ataxin-1
Spinocerebellar ataxia type 2	<i>ATXN2</i>	12q24.1	Ataxin-2
Spinocerebellar ataxia type 3 (Machado-Joseph disease)	<i>ATXN3</i>	14q21	Ataxin-3
Spinocerebellar ataxia type 6	<i>CACNA2A</i>	19p13.3	$\alpha_1\text{-Voltage-dependent calcium channel}$ subunit
Spinocerebellar ataxia type 7	<i>ATXN7</i>	3p14.1	Ataxin-7

## Others

**Q. Multifactorial disorders are:** (DMC – M. Phil, Diploma July, 2005)

- |                                |   |
|--------------------------------|---|
| a) cleft lip and palate        | T |
| b) spina bifida occulta        | T |
| c) Down's syndrome             | F |
| d) Congenital pyloric stenosis | T |
| e) Von willebrand disease      | F |

**HELP LINK:**

### Multifactorial disorders:

- |  |  |
|--|--|
| <ul style="list-style-type: none"> <li>• Cleft lip or cleft palate (or both)</li> <li>• Congenital heart disease</li> <li>• Coronary heart disease</li> <li>• Hypertension</li> <li>• Gout</li> <li>• Diabetes mellitus</li> <li>• Pyloric stenosis</li> </ul> | <ul style="list-style-type: none"> <li>• Club foot</li> <li>• Anencephaly</li> <li>• Meningomyelocele</li> <li>• Dislocation of hip</li> </ul> |
|--|--|

**Q. In a pair of homologous chromosomes (excepting the sex chromosomes): (BSMMU – MD/MS - 05Ja)**

- |  |   |
|--|---|
| A. the two chromosomes are usually of the same length                | T |
| B. the two chromosomes carry genetic information for the same traits | T |
| C. a total of two chromatids are seen during metaphase.              | F |
| D. genetic exchange usually occurs at more than one site.            | F |
| E. the two chromosomes bear identical genes at the same gene locus.  | T |

**Q. DNA is – (DMC - MD/MS -04Ja)**

- |                                     |   |
|-------------------------------------|---|
| A. component of chromosomes         | T |
| B. is found in the eukaryotic cells | T |
| C. contains bases uracil            | F |
| D. contains the sugar moiety ribose | T |
| E. is present in bacteria           | T |

**Q. In true hermaphroditism- (DMC - MD/MS -04Ja)**

- |  |   |
|--|---|
| a) both primordial follicles and seminiferous tubules are present in gonadal tissue. | T |
| b) chromosomal sex is usually female (46xx)  | T |
| c) mosaics do not occur  | F |
| d) mosaics occur   | T |
| e) external sex is usually female  | F |

**Q. DNA analysis can determine- (DMC - MD/MS -04Ja)**

- |   |   |
|---|---|
| a) Age                                      | F |
| b) Sex                                      | T |
| c) Absolute identification of an individual | T |
| d) Disputed paternity                       | T |
| e) Race                                     | F |

**HELP LINK:**

1. Identification of an individual, identical twins
2. Disputed paternity
3. Study of animal & human evolution.
4. Identifying chromosomal location of genes causing inherited disease

**Q. Ploidy analysis was studied by: (DMC - MD/MS -04Ja)**

- |                           |   |
|---------------------------|---|
| a) microspectrophotometry | F |
| b) cytofluorometry        | F |
| c) flow cytometry         | T |
| d) radio immunoassay      | F |
| e) ELISA method.          | F |

**Q. If a mutant gene is not expressed phenotypically in a person, this is said to represent (M. phil, Diploma – 03Ju)**

- |                          |   |
|--------------------------|---|
| a) Reduced penetrance    | T |
| b) Codominance           | F |
| c) Genetic heterogeneity | F |
| d) Variable expressivity | F |
| e) Nondisjunction        | F |

**Help link:**

**Reduced penetrance:** Inhibit the mutant gene but are phenotypically normal.

- Usually expressed in percentage.
- 50% penetrance means 50% of those who carry the gene express the trait.

(Ref: Robbins-9<sup>th</sup>, P-140)

**Co-dominance:** Both allele of a gene pair.

- Fully expressed in heterozygote state. e.g. ABO blood group, HLA.

**Genetic heterogeneity:** Mutation at several genetic loci may produce same trait.

**Q. Somatic cells of normal female – (BSMMU – MD/MS - 02Ja)**

- |   |   |
|---|---|
| a) Contain a single Barr body                     | T |
| b) Have karyotype 46 XX                           | T |
| c) Have one inactive Y and an active X chromosome | F |
| d) Are never diploid                              | F |
| e) Are viable without any sex chromosome          | F |

**Help link:** Sex determination can be done in somatic cells of female by karyotype; Sex chromatin/ Barr body.

**Q. Lethal mutations are: (DMC - MD/MS -01Ja)**

- |   |   |
|---|---|
| A. Substitution of adenine for cytosine.        | F |
| B. Substitution of cytosine for guanine.        | F |
| C. Substitution of methylcytosine for cytosine. | F |
| D. Deletion of three nucleotides.               | T |
| E. Insertion of one nucleotide.                 | T |

**3.5 Chromosome and contiguous gene disorders**

Disease	Locus	Incidence	Clinical features
<b>Numerical chromosomal abnormalities</b>			
Down's syndrome (trisomy 21)	47,XY,+21 or 47,XX,+21	1:800	Characteristic facies, IQ usually < 50, congenital heart disease, reduced life expectancy
Edwards' syndrome (trisomy 18)	47,XY,+18 or 47,XX,+18	1:6000	Early lethality, characteristic skull and facies, frequent malformations of heart, kidney and other organs
Patau's syndrome (trisomy 13)	47,XY,+13 or 47,XX,+13	1:15000	Early lethality, cleft lip and palate, polydactyly, small head, frequent congenital heart disease
Klinefelter's syndrome XYY	47,XXY 47,XYY	1:1000 1:1000	Phenotypic male, infertility, gynaecomastia, small testes (p. 766) Usually asymptomatic, some impulse control problems
Triple X syndrome	47,XXX	1:1000	Usually asymptomatic, may have reduced IQ
Turner's syndrome	45,X	1:5000	Phenotypic female, short stature, webbed neck, coarctation of the aorta, primary amenorrhoea (p. 765)
<b>Recurrent deletions, microdeletions and contiguous gene defects</b>			
Di George/ velocardiofacial syndrome	22q11.2	1 in 4000	Cardiac outflow tract defects, distinctive facial appearance, thymic hypoplasia, cleft palate and hypocalcaemia. Major gene seems to be <i>TBX1</i> (cardiac defects and cleft palate)
Prader–Willi syndrome	15q11–q13	1:15000	Distinctive facial appearance, hyperphagia, small hands and feet, distinct behavioural phenotype. Imprinted region, deletions on paternal allele in 70% of cases
Angelman's syndrome	15q11–q13	1:15000	Distinctive facial appearance, absent speech, EEG abnormality, characteristic gait. Imprinted region, deletions on maternal allele in <i>UBE3A</i>
Williams' syndrome	7q11.23	1:10000	Distinctive facial appearance, supravalvular aortic stenosis, learning disability and infantile hypercalcemia. Major gene for supravalvular aortic stenosis is <i>elastin</i>
Smith–Magenis syndrome	17p11.2	1 in 25 000	Distinctive facial appearance and behavioural phenotype, self-injury and rapid eye movement (REM) sleep abnormalities. Major gene seems to be <i>RAH</i>

(Ref: Davidson-23<sup>rd</sup>)

**Some important MCQs****Q. Autosomal dominant diseases which are important to surgeons include:**

- a) hereditary spherocytosis
- b) haemophilia
- c) Von Recklinghausen's disease
- d) familial agammaglobulinaemia
- e) mucoviscidosis

Ans.

- a) **True** Congenital spherocytosis (spherocytic haemolytic anaemia) is due to the erythrocytes being more nearly spherical than normal. The result is a condition in which the life span of the erythrocytes is reduced. The abnormal cells are sequestered in the spleen. Clinically, anaemia, intermittent jaundice and increasing splenomegaly occur.
- b) **False** Although haemophilia is a disease of considerable surgical importance it is rare, affecting only 6 per 100000 of the population. It is inherited as a sex-linked recessive Mendelian trait although sporadic cases do occur. It is transmitted to males by asymptomatic females who themselves possess a normal level of AHG of between 60—75% of the mean. Males with an AHG level of 25% of the mean can live a normal life but will bleed after major trauma, but when the level falls to between 1—5% minor trauma causes bleeding and haemoarthroses develop, these last occurring after very minor injuries when the level is less than 1%.
- c) **True** Von Recklinghausen's disease, otherwise known as neurofibromatosis, is associated with multiple nodules on the peripheral, and in some cases along the visceral branches of the sympathetic nerves. The disease is frequently associated with multiple pigmented patches of the skin, the café au lait spots. The various manifestations of this disease include:
- (a) Multiple subcutaneous nodules associated with café au lait spots
  - (b) Dumb-bell tumours of the spinal nerves
  - (c) Acoustic nerve neuroma
  - (d) Elephantiasis neurothatoza
  - (e) Plexiform neuromata
- d) **False** Otherwise known as infantile sex-linked hypogammaglobulinaemia this condition may exist in the presence of normal cell-mediated immunity. It is, however, inherited as an X-linked recessive. Affected males have no B cells in their blood or lymphoid tissues and consequently their lymph nodes are small and they have no tonsils. IgA, IgM, IgD or IgE is not present in the serum. For the first 6 months of life, such infants are protected from infection by their maternal IgG which crossed the placenta. After this, in the absence of protection, the affected males develop recurrent pyogenic infections.
- e) **False** This condition is inherited as autosomal recessive. To the surgeon this condition presents with congenital intestinal obstruction, the muscular power of the intestine being insufficient to propel the viscid meconium. To the paediatrician milder forms of the condition present with failure of the affected infant to thrive and recurrent pulmonary infections.

(Ref: Smiddy)

**Q. Chromosome abnormalities may occur:**

- a) in Klinefelter's syndrome
- b) following treatment with methotrexate
- c) as a result of ionising radiation
- d) in Down's syndrome
- e) in Christmas disease

Ans.

- a) **True** This is one of the most frequent forms of genetic disease and hypogonadism involving the sex chromosomes. It occurs in approximately 1:850 live births. Its presence is rarely recognised before puberty, at which point the absence of testicular and penile enlargement becomes increasingly obvious. FSH levels are consistently elevated and the testosterone levels reduced.
- b) **False** Methotrexate does not directly affect the chromosomes.
- c) **True** Ionising radiation produces both 'sticky' chromosomes and breaks in the chromosomes, causing difficulties in the separation of the chromatids at anaphase.

- d) **True** Otherwise known as Trisomy 21, Down's syndrome is the commonest form of chromosomal disorder and a significant cause of mental retardation. In Trisomy 21, the extra chromosome results in a chromosome count of 47, although rarely the condition can arise from the translocation of chromosomal material leaving the chromosomal count at the normal figure of 46. The incidence of Down's is closely linked to maternal age, the condition occurring with increasing frequency with the advancing age of the mother, so that over 45 it affects 1:25 live births. This suggests that the primary fault lies in the ovum.

e) **False** Christmas disease is clinically similar to haemophilia. It is not, however, associated with any chromosomal abnormality.

(Ref: Smiddy)

## ENVIRONMENTAL & NUTRITIONAL DISEASES

**Q. Heavy metals toxic to human health are (BSMMU –Residency - MD/MS, Basic science, Paediatrics, Dentistry – March '19)**

- a) lead
- b) copper
- c) mercury
- d) selenium
- e) cadmium

Ans. a) T b) F c) T d) F e) T

**Help Link:** Lead, mercury, arsenic, and cadmium

(Ref: Robbins-9<sup>th</sup>, P-410)

**Q. Diseases arising from occupational exposure are (BSMMU –Residency – Dentistry – March '18)**

- a) acrodermatitis enteropathica
- b) acute leukemia
- c) arsenicosis
- d) asbestosis
- e) aspergillosis

Ans. a) F b) T c) T d) T e) F

(Ref: Davidson 23<sup>rd</sup>, P-1320)

**Q. Secondary amyloidosis can occur in (BSMMU – Non-Residency – MD, Basic science – July' 15)**

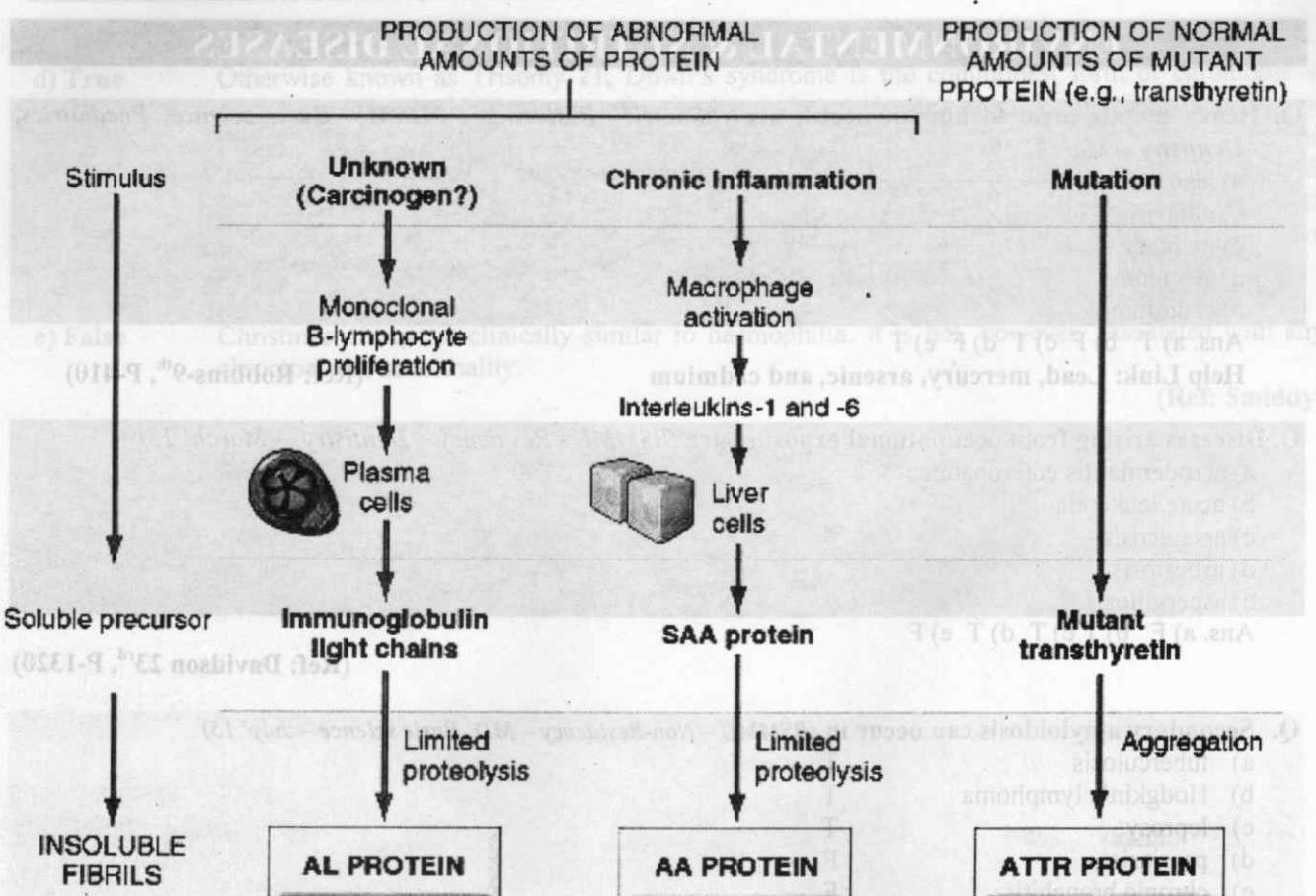
- |                       |   |
|-----------------------|---|
| a) tuberculosis       | T |
| b) Hodgkin's lymphoma | T |
| c) leprosy            | T |
| d) psoriasis          | F |
| e) chronic bronchitis | F |

**Help link:**

Amyloidosis is a systemic disease which results from abnormal folding of proteins, which are deposited as fibrils in extracellular tissues and disrupt normal function.

### Pathogenesis:

CLASSIFICATION OF AMYLOIDOSIS			
SYSTEMIC (GENERALIZED) AMYLOIDOSIS			
Primary, idiopathic	AL	Multifocal myelomas and other monoclonal plasma cell disorders	Immunoglobulin deposits (primary amyloidosis)
SAA	AA	Chronic inflammatory conditions	Reactive systemic amyloidosis (secondary amyloidosis)
B-microglobulin	mAG	Chronic renal disease	Hemodialysis-associated amyloidosis
HEREDITARY AMYLOIDOSIS			
	AA		Familial Mediterranean fever
Transfusional	ATTR		Familial amyloidotic neuropathy (sweat type)
Transfusional	ATTR		SYSTEMIC SERINE AMYLOIDOSIS



**FIGURE:** Pathogenesis of amyloidosis, showing the proposed mechanisms underlying deposition of the major forms of amyloid fibrils.

(Ref: Robin's & Cotran's-9<sup>th</sup>, P-258)

#### Classification of Amyloidosis:

Clinicopathologic Category	Associated Diseases	Major Fibril Protein	Chemically Related Precursor Protein
<b>SYSTEMIC (GENERALIZED) AMYLOIDOSIS</b>			
Immunocyte dyscrasias with amyloidosis (primary amyloidosis)	Multiple myeloma and other monoclonal plasma cell proliferations	AL	Immunoglobulin light chains, chiefly $\lambda$ type
Reactive systemic amyloidosis (secondary amyloidosis)	Chronic inflammatory conditions	AA	SAA
Hemodialysis-associated amyloidosis	Chronic renal failure	$\text{A}\beta_2\text{m}$	$\beta_2$ -microglobulin
<b>HEREDITARY AMYLOIDOSIS</b>			
Familial Mediterranean fever		AA	SAA
Familial amyloidotic neuropathies (several types)		ATTR	Transthyretin
<b>SYSTEMIC SENILE AMYLOIDOSIS</b>		ATTR	Transthyretin

Clinicopathologic Category	Associated Diseases	Major Fibril Protein	Chemically Related Precursor Protein
<b>LOCALIZED AMYLOIDOSIS</b>			
Senile cerebral	Alzheimer disease	Ab	APP
Endocrine		A Cal	Calcitonin
Medullary carcinoma of thyroid	Type 2 diabetes	AIAPP	Islet amyloid peptide
Islets of Langerhans		AANF	Atrial natriuretic factor
Isolated atrial amyloidosis			

(Ref: Robin's & Cotran's-9<sup>th</sup>, P-259)

### Lead poisoning

**Q. Effects of lead poisoning in children are (BSMMU -Residency – MD, MS, Basic Science – March' 18)**

- a) impaired peripheral nerve function
- b) decreased level of erythrocyte protoporphyrin
- c) increased vitamin D metabolism
- d) encephalopathy
- e) nephrotoxicity

Ans. a) T b) F c) F d) T e) T

**Q. Lead poisoning leads to: (BSMMU – MS - January, 2010)**

- |                          |   |
|--------------------------|---|
| a) fatty change in liver | F |
| b) microcytic anaemia    | T |
| c) encephalopathy        | T |
| d) intestinal colic      | T |
| e) thrombo-embolism      | F |

### HELP LINK:

metabolic syndrome

4. Lipoprotein (A)

5. Factors affecting hemostasis e.g. fibrinogen, platelet derived factors etc.

6. Other factors:

- Lack of exercise
- Competitive, stressful life style ("type A" personality)
- Obesity (which is often associated with hypertension, diabetes, hypertriglyceridemia, and decreased HDL)
- Postmenopausal estrogen deficiency
- High Ch O/H ratio

### SOURCES

NON-CORONAROID

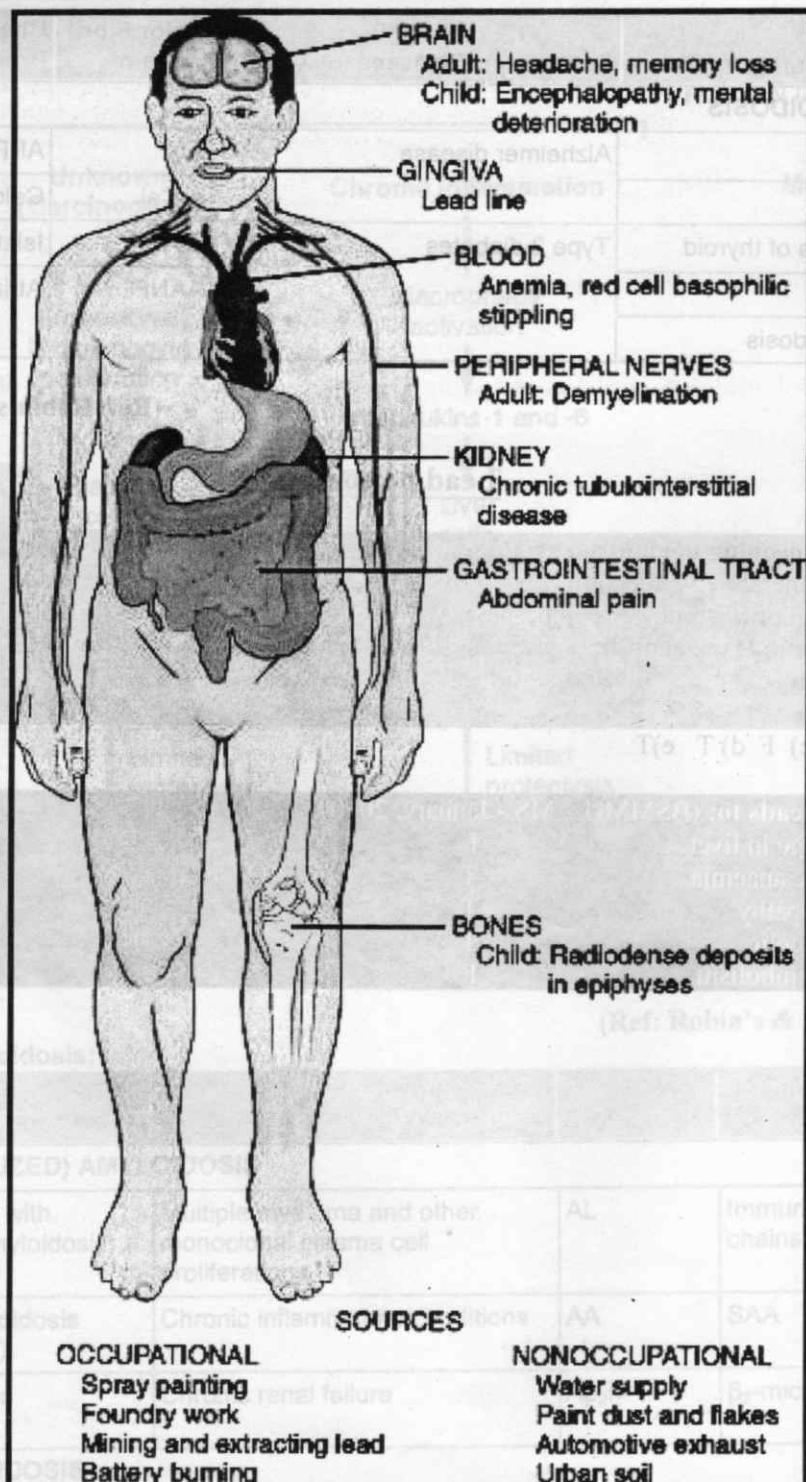


FIGURE: Pathologic features of lead poisoning in adults.

(Ref: Robbins & Cotran-9<sup>th</sup>, P-411)

## Systemic Pathology

### Blood vessels

**Q. Major risk factors associated with development of coronary atherosclerosis include (M. phil, Diploma (DMC) – 03Ju)**

- |                       |   |
|-----------------------|---|
| a) Elevated HDL       | F |
| b) Cigarette smoking  | T |
| c) Diabetes mellitus  | T |
| d) Hypertension       | T |
| e) Type A personality | F |

#### **HELP LINK:**

#### **■ Risk factors of atherosclerosis:**

##### **Major risk factors:**

###### **Non-modifiable:**

1. Genetic abnormalities
2. Family history
3. Increasing age
4. Male gender

###### **Modifiable:**

1. Hyperlipidaemia
2. Hypertension
3. Cigarette smoking.
4. Diabetes
5. Inflammation

##### **Additional risk factors:**

1. C-reactive protein
2. Hyperhomocystinemia
3. Metabolic syndrome
4. Lipoprotein (a)
5. Factors affecting hemostasis e.g. thrombin, platelet-derived factors etc.
6. Other factors:
  - Lack of exercise
  - Competitive, stressful life style ("type A" personality)
  - Obesity (which is often associated with hypertension, diabetes, hypertriglyceridemia, and decreased HDL).
  - Postmenopausal estrogen deficiency
  - High CHO intake
  - Alcohol
  - Hardened unsaturated fat intake
  - *Chlamydia pneumoniae* (Ref: Robbin's & Cotran-9<sup>th</sup>, P-492 + 8<sup>th</sup>, P-496-498)

**Q. Tumours of blood vessels include- (BSMMU-MS-05Ja)**

- A. Glomus tumour
- B. Angiosarcoma
- C. Adenoma
- D. Kaposi's sarcoma
- E. Squamous cell carcinoma

Ans.

A. True (*It is a biologically benign but often exquisitely painful tumour that arises from the modified smooth muscle cells of glomus body, a specialized arteriovenous anastomosis that is involved in autoregulation*)

B. True (*It is a malignant neoplasm*)

C. False

D. True (*It is an intermediate grade neoplasm*)

E. False

**HELP LINK:**

<b>Classification of Vascular Tumors and Tumor-like Conditions</b>	
<b>Benign Neoplasia., Developmental and Acquired Condition</b>	
<b>Hemangioma</b>	
Capillary hemangioma	
Cavernous hemangioma	
Pyogenic granuloma (lobular capillary hemangioma)	
<b>Lymphangioma</b>	
Simple (capillary) lymphangioma	
Cavernous lymphangioma (cystic lymphangioma)	
Glomus tumour	
<b>Vascular ectasias</b>	
Nevus flammeus	
Spider telangiectasia (arterial spider)	
Hereditary hemorrhagic telangiectasis (Osler-Weber-Rendu disease)	
<b>Reactive vascular proliferations</b>	
Bacillary angiomatosis	
<b>Intermediate-Grade Neoplasms</b>	
Kaposi's sarcoma	
Hemangiendothelioma	
<b>Malignant Neoplasms</b>	
Angiosarcoma	

**Q. Langerhan's cells originate from: (PG-96Ja)**

- A. Schwann cells F
- B. Lymphocytes F
- C. Primitive cells T
- D. Melanocytes F

**FIGURE: Pathologic features of lead poisoning in adults.**

(Ref: Robbins & Cotran-9<sup>th</sup>, P-631)

## The Heart

**Q. In a case of myocardial infarction: (BSMMU - M. Phil, Diploma – July '10)**

- |  |   |
|--|---|
| a) Necrosis is gangrenous in nature                              | F |
| b) Morphological changes are reversible                          | F |
| c) Thrombus may develop in cardiac chambers                      | T |
| d) Reperfusion injury occurs if thrombolysis done after 24 hours | T |
| e) Repair occurs by fibrosis                                     | T |

**HELP LINK:**

The dominant histologic characteristic of infarction is ischemic coagulative necrosis. It is important to recall that if the vascular occlusion has occurred shortly (minutes to hours) before the death of the patient, no demonstrable histologic changes may be evident; if the patient survives even, 12 to 18 hours, the only change present may be hemorrhage.

An inflammatory response begins to develop along the margins of infarcts within a few hours and is usually well defined within 1 or 2 days. Inflammation at these sites is incited by the necrotic material; given sufficient time, there is gradual degradation of the dead tissue with phagocytosis of the cellular debris by neutrophils and macrophages. Eventually the inflammatory response is followed by a reparative response beginning in the preserved margins. In stable or labile tissues, some parenchymal regeneration may occur at the periphery where the underlying stromal architecture has been spared. However, most infarcts are ultimately replaced by scar tissue. The brain is an exception to these generalizations; as with all other causes of cell death, ischemic injury in the central nervous system results in liquefactive necrosis.

**Q. Following statements are true for brown atrophy: (BSMMU - M. Phil, Diploma – July '10)**

- |   |   |
|---|---|
| a) it occurs in liver   | F |
| b) it occurs in heart in old age                                | T |
| c) lipofuscin granule give the colour brown                     | T |
| d) autophagic granules are present within cell cytoplasm.       | T |
| e) autophagic granules are nothing but the lipofuscin granules. | T |

**HELP LINK:**

With advancing age the amount of epicardial fat increases, particularly over the anterior surface of the right ventricle and in the atrial septum. A reduction in the size of the left ventricular cavity, particularly in the base-to-apex dimension, is associated with increasing age and accentuated by systemic hypertension. Accompanied by a rightward shift and tortuosity of a dilated ascending aorta, this chamber alteration causes the basal ventricular septum to bend leftward, bulging into the left ventricular outflow tract (termed sigmoid septum). Such reduction in the size of the left ventricular cavity can simulate the obstruction to blood leaving the left ventricle that often occurs with hypertrophic cardiomyopathy.

Several changes of the valves are noted with aging, including calcification of the mitral annulus and aortic valve, the latter frequently leading to aortic stenosis. In addition, the valves can develop fibrous thickening, and the mitral leaflets tend to buckle back toward the left atrium during ventricular systole, simulating a prolapsing (myxomatous) mitral valve. Moreover, many older persons develop small filiform processes (Lambl excrescences) on the closure lines of aortic

and mitral valves, probably arising from the organization of small thrombi on the valve contact margins.

Compared with younger myocardium, 'elderly' myocardium also has fewer myocytes, increased collagenized connective tissue and, in some individuals, deposition of amyloid. In the muscle cells, lipofuscin deposits, and basophilic degeneration, an accumulation within cardiac myocytes of a gray-blue byproduct of glycogen metabolism, may be present. Extensive lipofuscin deposition in a small, atrophied heart is called **brown atrophy**; this change often accompanies cachectic weight loss, as seen in terminal cancer.

Although the morphologic changes described are common in elderly patients at necropsy, and they may mimic disease, in only a minority are they associated with clinical cardiac dysfunction.

## GIT

**Q. Conditions that may lead to development of colon cancer (BSMMU – Residency - MD, MS, Basic Science, Dentistry - March '17)**

- a) Crohn disease
- b) colonic diverticula
- c) ulcerative colitis
- d) sessile serrated adenoma of colon
- e) amoebiasis

**Ans. a) T b) F c) T d) T e) F**

**Help link:**

■ **Risk factors for colorectal carcinoma:**

1. Age: Incidence peaks at 60 to 70 years of age, and fewer than 20% of cases occur before age 50.
2. Sex: Males are affected slightly more than female.
3. Excessive dietary caloric intake relative to requirement
4. Low intake of unabsorbable vegetable fibre.
5. High intake of refined carbohydrates and fat
6. Increased intake of red meat
7. Decreased intake of protective micronutrients.

**(Ref: Robbins & Cotran-9<sup>th</sup>, P-807)**

**Q. Risk factors of colorectal cancers include (BSMMU – Non-Residency – MD, MS, Basic science – July' 16)**

- |                         |   |
|-------------------------|---|
| a) obesity              | T |
| b) dietary calcium      | F |
| c) dietary selenium     | F |
| d) saturated animal fat | T |
| e) adenomatous polyp    | T |

**Q.** A surgeon planned colectomy on a 75 year old female who has a 5 cm sessile mucosal mass in the lower sigmoid colon. Which of the following technical supports will help in better management of this case: (BSMMU – MD – January, 2010)

- |                                   |   |
|-----------------------------------|---|
| a) FNAC                           | F |
| b) Direct immunofluorescence test | F |
| c) Frozen section                 | T |
| d) Stool occult blood test        | T |
| e) Serum .CEA assay               | T |

### Breast

**Q.** Painless firm right axillary lymphadenopathy is found in a 44 years old female on physical examination. Which of the following conditions are most likely to be present: (BSMMU – MD – January, 2010)

- |                               |   |
|-------------------------------|---|
| a) hidradenitis suppurative   | T |
| b) ductal carcinoma of breast | T |
| c) malignant melanoma of hand | F |
| d) leiomyosarcoma of uterus   | F |
| e) acute mastitis             | T |

### Male & Female genitalia

**Q.** Germ cell tumours of ovary are (BSMMU – Non-Residency – MS, Basic science – July' 18)

- a) teratoma
- b) seminoma
- c) dysgerminoma
- d) mucinous cystadenoma
- e) Krukenburg's tumour

Ans. a) T b) F c) T d) F e) F

#### HELP LINK:

##### Pathologic classification of common testicular tumors:

###### A. GERM CELL TUMORS:

###### Seminomatous tumors:

- Seminoma
- Spermatocytic seminoma

###### Non-seminomatous tumors:

- Embryonal carcinoma
- Yolk sac (endodermal sinus) tumor
- Choriocarcinoma

###### Teratomas

**B. SEX CORD - STROMAL TUMORS:**

- Leydig cell tumor
- Sertoli cell tumor

(Ref: Robbins & Cotran-9<sup>th</sup>, P-975)**■ Gem cell tumors of ovary:**

a. Teratoma:

- Immature
- Mature:
  - Solid
  - Cystic (dermoid cyst)
- Monodermal (e.g. struma ovarii, carcinoid)

b. Dysgerminoma

c. Yolk sac tumor (endodermal sinus tumor)

d. Mixed germ cell tumors

(Ref: Robbins & Cotran-9<sup>th</sup>, P-1023)**Q. The following are considered as germ cell tumours:** (BSMMU - M. Phil, Diploma, July-09)

- |                              |   |
|------------------------------|---|
| a) Seminoma                  | T |
| b) Teratoma                  | T |
| c) Choriocarcinoma           | T |
| d) Malignant melanoma        | F |
| e) Transition cell carcinoma | F |

**Q. Germ cell tumors are -** (MD/MS (DMC)-09Ja)

- |                                    |   |
|------------------------------------|---|
| a) teratoma                        | T |
| b) disgerminoma                    | T |
| c) androblastoma                   | F |
| d) seminoma                        | T |
| e) non gestational choriocarcinoma | T |

**Q. The following tumours are of embryonic origin -** (MD/MS (DMC)-09Ja)

- |                           |   |
|---------------------------|---|
| a) dermoid cyst           | F |
| b) nephroblastoma         | T |
| c) glioblastoma           | F |
| d) reticular cell sarcoma | F |
| e) retinoblastoma         | T |

**Q. Teratomas:** (BSMMU-MS-06Ja)

- A. may originate outside the gonads
- B. of the testis are unable to produce HCG
- C. can be benign
- D. may show extra-embryonic differentiation
- E. have a peak incidence in the sixth decade

Ans.

- A. True** (They arise from totipotent cells and so are principally encountered in gonads; they occur rarely in sequestered primitive cell rests elsewhere)
- B. False** (In the postpubertal male, all teratomas are regarded as malignant and capable of producing HCG)
- C. True** (e.g. Dermoid cyst)
- D. True**
- E: False** (Pure forms of teratomas are fairly common in infants and children)

**Q. The following tumours are germ cell tumors- (BSMMU-Sur-04Ja)**

- |                             |   |
|-----------------------------|---|
| a) Brenner tumour           | F |
| b) Dysgerminoma             | T |
| c) Arrhenoblastoma          | F |
| d) Embryonal cell carcinoma | T |
| e) choriocarcinoma          | T |

**HELP LINK:**

Testis	Ovary
1. Seminoma	1. Teratoma
2. Embryonal carcinoma	2. Dysgerminoma
3. Teratoma	3. Choriocarcinoma
4. Choriocarcinoma	4. Yolk sac tumor
5. Yolk sac tumor	
6. Spermatocytic seminoma	
7. Polyembryoma & mixed pattern	

**Q. Tumours of germ all include-(BSMMU-MD - 02Ja)**

- |                          |   |
|--------------------------|---|
| a) Seminoma              | T |
| b) Mucoepidermoid tumour | F |
| c) Dermoid cyst          | T |
| d) Polyembryoma          | T |
| e) Krukenberg's tumour.  | F |

**HELP LINK:**

Testis	Ovary
1. Seminoma	1. Teratoma
2. Embryonal carcinoma	2. Dysgerminoma
3. Teratoma	3. Choriocarcinoma
4. Choriocarcinoma	4. Yolk sac tumor
5. Yolk sac tumor	
6. Spermatocytic seminoma	
7. Polyembryoma & mixed pattern	

**Q. Tumours of germ all include- (BSMMU-MS-02Ja)**

- |                          |   |
|--------------------------|---|
| a) Seminoma              | T |
| b) Mucoepidermoid tumour | F |
| c) Dermoid cyst          | T |
| d) Polyembryoma          | T |
| e) Krukenberg's tumour.  | F |

### Female genital organs

**Q. Followings are malignant ovarian tumor (BSMMU – Non-Residency – MS, Basic Science – July' 17)**

- a) dysgerminoma
- b) endodermal sinus tumor
- c) solid teratoma
- d) granulosa cell tumor
- e) Brenner's tumor

Ans. a) T b) T c) T d) F e) F

**Help link:**

**WHO Classification of Ovarian Neoplasms:**

**A. Surface epithelial-stromal tumors:**

**a. Serous tumors:**

- Benign (cystadenoma)
- Borderline tumors (serous borderline tumor)
- Malignant (serous adenocarcinoma)

**b. Mucinous tumors (endocervical-like & intestinal type):**

- Benign (cystadenoma)
- Borderline tumors (mucinous borderline tumor)
- Malignant (mucinous adenocarcinoma)

**c. Endometrioid tumors:**

- Benign (cystadenoma)
- Borderline tumors (endometrioid borderline tumor)
- Malignant (endometrioid adenocarcinoma)

**d. Clear cell tumors:**

- Benign
- Borderline tumors
- Malignant (clear cell adenocarcinoma)

**e. Transitional cell tumors:**

- Brenner tumor
- Brenner tumor of borderline malignancy
- Malignant Brenner tumor
- Transitional cell carcinoma (non- Brenner type)

**f. Epithelial –stromal:**

- Adenosarcoma
- Malignant mixed mullerian tumor

**B. Sex cord-stromal tumors:**

- Granulosa tumors
- Fibromas
- Fibrothecomas
- Thecomas
- Sertoli-Leydig cell tumors
- Steroid (lipid) cell tumors

Chondrosarcoma

(LCH)

**C. Germ cell tumors:****a. Teratoma:**

- Immature
- Mature:
  - Solid
  - Cystic (dermoid cyst)
- Monodermal (e.g. struma ovarii, carcinoid)

**b. Dysgerminoma****c. Yolk sac tumor (endodermal sinus tumor)****d. Mixed germ cell tumors****D. Metastatic cancer from non-ovarian primary:**

- Colonic, appendiceal
- Gastric
- Pancreaticobiliary
- Breast

(Ref: Robbins & Cotran-9<sup>th</sup>, P-1023)**Q. Sex-cord stromal tumours are (BSMMU – Non-Residency – MD, MS, Basic science, Dentistry – July' 16)**

- |                          |   |
|--------------------------|---|
| a) dysgerminoma          | F |
| b) fibroma               | T |
| c) teratoma              | F |
| d) granulosa cell tumour | T |
| e) adenocarcinoma        | F |

**Q. Functional tumours of the ovaries are: (BSMMU-MS-06Ja)**

- A. Hillus cell tumour
- B. Dysgerminoma
- C. Chorio-carcinoma
- D. Seminoma
- E. Teratoma

Ans.

- A. True** (The most consistent laboratory finding is an elevated 17-ketosteroid excretion level unresponsive to cortisone suppression; almost always benign; patients present with evidence of masculinization, hirsutism, voice changes and clitorial enlargement)
- B. True** (Most of the tumour have no endocrine function, A few produce elevated levels of HCG.)
- C. True** (Like all choriocarcinomas, ovarian choriocarcinomas elaborate high levels of HCG that are sometimes helpful in establishing the diagnosis)
- D. True** (Seminoma is functional tumour of testis, its ovarian counterpart is known as dysgerminoma)
- E. False** (Benign teratomas or dermoid cysts, give rise to no hormonal secretions but monodermal teratomas of ovary are a group ovarian tumours the most common of which are struma ovarii and carcinoid both of which are functional and may develop hyperthyroidism and carcinoid syndrome respectively)

(Ref: Smiddy)

**Q. Hormone producing tumour of the ovary include- (BSMMU-Sur-04Ja)**

- |                          |                       |
|--------------------------|-----------------------|
| a) Granulosa cell tumour | T                     |
| b) Teratoma              | F                     |
| c) Mucinous cell tumour  | F                     |
| d) Chorio-carcinoma      | T                     |
| e) Hilus cell tumour     | T (Leydig cell tumor) |

**Bones****Q. Malignant tumours of bone include (BSMMU -Residency – MS, Basic Science, Dentistry – March' 16)**

- |                    |   |
|--------------------|---|
| a) exostosis       | F |
| b) chondrosarcoma  | T |
| c) Ewing's tumor   | T |
| d) osteosarcoma    | T |
| e) osteoid osteoma | F |

**HELP LINK:**

- Epithelial stromal
- Adenocarcinoma
- Malignant mixed mesodermal tumor

**A. Primary bone tumors:**

Histologic type	Benign	Malignant
<b>Hematopoietic (40%)</b>	-	Myeloma Malignant lymphoma
<b>Chondrogenic (22%)</b>	Osteochondroma Chondroma Chondroblastoma Chondromyxoid fibroma	Chondrosarcoma Dedifferentiated chondrosarcoma Mesenchymal chondrosarcoma
<b>Osteogenic (19%)</b>	Osteoid osteoma Osteoblastoma	Osteosarcoma
<b>Fibrogenic</b>	Fibrous cortical defect (fibroma) Non-ossifying fibroma Fibrous histiocytoma Desmoplastic fibroma	Fibrosarcoma
<b>Unknown origin (10%)</b>	Giant cell tumor Unicameral cyst Aneurysmal bone cyst	Ewing tumor Giant cell tumor Adamantinoma
<b>Neuroectodermal</b>	-	Ewing sarcoma
<b>Notochordal</b>	Benign notochordal cell tumour	Chordoma

(Ref: Robbins & Cotran – 9<sup>th</sup>, P-1197)**B. Secondary bone tumors (Metastatic tumors):****1. In adults- From the cancers of-**

- Prostate
- Breast
- Kidney
- Lung
- Thyroid

**2. In child - From-**

- Neuroblastoma
- Wilms tumor
- Osteosarcoma
- Ewing sarcoma
- Rhabdomyosarcoma.

(Ref: Robbins & Cotran – 9<sup>th</sup>, P-1179)

**Q. Primary malignant tumours of bone:** (BSMMU – M. Phil, Diploma (Non-Residency)-  
11Ju, DMC & others – MD/MS – 11Ju)

- |                              |   |
|------------------------------|---|
| a) osteogenic sarcoma        | T |
| b) fibrous dysplasia         | F |
| c) giant cell tumour of bone | T |
| d) multiple myeloma          | T |
| e) ewings tumour             | T |

**Q. Multiple ossification centers in the epiphysis are seen in-** (BSMMU-MS-07Ja)

- |                             |   |
|-----------------------------|---|
| a) Syphilis                 | T |
| b) Cleido-cranial dysplasia | T |
| c) Down's syndrome          | F |
| d) Scurvy                   | F |
| e) Cretinism                | F |

**Q. Following are the malignant bone tumors-** (BSMMU-Med/Sur-01Ja)

- |                     |   |
|---------------------|---|
| a) Multiple myeloma | F |
| b) Osteoblastoma    | F |
| c) Osteoid osteoma  | F |
| d) Ewing's tumour   | T |
| e) Osteosarcoma     | T |

### Adrenal gland

**Q. Tumors of chromaffin cells of adrenal medulla -** (M. phil, Diploma (DMC) – 03,July)

- a) ganglioneuroma
- b) phaeochromocytoma
- c) neuroblastoma
- d) wilms tumor
- e) carcinoid syndrome.

Ans.

- a) F
- b) T
- c) F (Common extracranial neoplasm)
- d) F (Most common primary renal tumour of childhood)
- e) F (Bronchial adenoma,Pancreatic carcinoma,Gastric carcinoma)

## CLINICAL PATHOLOGY

**Q. Pyuria with negative urine culture are found in** (BSMMU – Non-Residency – MD, MS, Basic Science & Dentistry – July' 17)

- a) renal tuberculosis
- b) salmonellosis
- c) leptospirosis
- d) patient under antibiotic treatment
- e) diabetes mellitus

Ans. a) T b) F c) F d) T e) F

**Help link:****The causes of sterile pyuria include**

- Treated urinary tract infection (UTI) within 2 weeks of treatment/inadequately treated (UTI)
- UTI with fastidious culture requirement
- renal stones
- prostatitis
- chlamydia urethritis
- renal papillary necrosis (e.g. from analgesic excess)
- tubulo-interstitial nephritis
- genitourinary tuberculosis (always consider - do 3 early morning urines)
- interstitial cystitis
- urinary tract neoplasm
- polycystic kidney

**Q Examination of ascitic fluid for malignant cell: (BSMMU – MD – January, 2010)**

- |  |   |
|--|---|
| a) is called FNAC                                  | F |
| b) is done on leishman stained slides              | F |
| c) is highly accurate process                      | F |
| d) needs fresh specimen                            | T |
| e) is often positive in advanced gastric carcinoma | T |

**HELP LINK:****Regarding study of ascitic fluid:**

- Ascitic fluid total protein concentration below 25g/L indicates transudative ascites.
- (Serum albumin- Ascitic fluid albumin)  $> 11$  /L strongly suggest portal HTN and cirrhosis (transudative ascites).
- Ascitic fluid total protein concentration above 25 g/L indicates exudative ascites.
- (Serum albumin- Ascitic fluid albumin)  $< 11$  g/L indicates exudative ascites.
- Ascites amylase activity above 1000 U/L identifies pancreatic ascites.
- Low ascites glucose concentrations suggest malignant disease or tuberculosis.
- Presence of malignant cells indicates intra-abdominal malignancy.
- Polymorphonuclear leucocyte count above  $250 \times 10^6$ /L strongly suggest (infection spontaneous bacterial peritonitis).

**Q. In nephrotic syndrome - (BSMMU-MS-07Ja)**

- |   |   |
|---|---|
| a) ECF volume increases                 | T |
| b) ECF osmolarity decreases             | T |
| c) Body Na content decreases            | F |
| d) Interstitial fluid volume decrease   | F |
| e) Effective circulatory vol. decreases | T |

**Q. Proteinuria is a feature of: (BSMMU-MS-05Ja)**

- A. Mercury poisoning
- B. Hypernephroma
- C. Cirrhosis of liver
- D. Cushing's syndrome
- E: Nephrotic syndrome

Ans.

- A. **True** (Proteinuria & nephrotic syndrome are observed rarely)
- B. **False** (May produce paraneoplastic syndrome due to abnormal hormone production may be associated with polycythaemia, hypercalcaemia, hypertension, hepatic dysfunction, feminization or masculinization, cushing syndrome, eosinophilia, leukaemoid reactions and amyloidosis)
- C. **False** (Protein synthesis is reduced & there is hypoalbuminaemia)
- D. **False** (Usually not associated with proteinuria)
- E. **True** (It causes massive proteinuria)