CELL AND TISSUE DAMAGE

Lesion (alteration) is a change in the cell structure, intercellular substance, tissues, and organs accompanied by disturbances in their vital activity.

There are different morphological manifestations of a lesion in the cells and tissues. Subcellular alteration, which largely occurs as a response to more of less constant stimuli and intracellular accumulation of a number of substances, due to the disturbances in cellular metabolism or excessive storage, as well as cell death (necrosis and apoptosis) have been described in the cells.

Two types or stages of lesions in the tissues have been described: degeneration and necrosis.

CELLULAR INJURY

Visible changes occur in the cells as a result of noxious agents, the degree of changes varying with the severity of the damaging processes: with minor damage the repair mechanisms changes, more severe damage results in cell death. There are a lot of genetic and acquired causes of cell injury.

Genetic causes of cellular injury producing disease may result from one of the following abnormalities:

1. Abnormalities of chromosomes. 2. Abnormalities of genes carried by chromosomes. 3. Disorders with multifactorial inheritance. 4. Disorders with variable genetic pattern.

Abnormalities of chromosomes

There are abnormalities in the number and/or morphology of chromosomes.

During meiosis in gametogenesis, two homologous chromosomes rather than moving to the opposite poles of the dividing cell, instead move to the same side so that one germ cell receives both chromosomes and the other germ cell none. This is referred to as **chromosomal disjunction**. The main examples of chromosomal nondisjunction are: Turner's syndrome (monosomy 45, XO), Klinefelter's syndrome (trisomy 47, XXY), Down's syndrome (trisomy 21 involving autosome 21).

When one homologous chromosome in meiosis or one chromatid in mitosis fails to reach the pole of dividing cell and is left out of the nucleus of the daughter cell, it is called **anaphase lag**. This results in one normal daughter cell and the other with monosomy.

A great deal of inherited and acquired structural abnormalities of the chromosomes have been described.

Translation means transfer of a segment of one chromosome to another nonhomologous chromosome. It may be of either of the following types: 1) balanced translocation, when the two fragments of chromosomes exchange material without any loss of material; 2) robertsonian translocation, when two acrocentric chromosomes lose their short arms and fuse at the centromere so that eventually the cell is left with 45 chromosomes.

Deletion means loss of part of the DNA from a chromosome. Deletion may be from terminal or middle portion of the chromosome. When both ends of a chromosome are lost and the two damaged ends join together, they form a ring chromosome.

Abnormalities of genes carried by chromosomes

Mendelian disorders are the result of mutation of a single gene of large effect. The term mutation refers to heritable alteration in the genome, more often affecting a single base in the gene so that protein synthesis is interfered with. The common types of mutations are point mutation and frameshift mutation. Mutations may be inherited from a parent, or may occur as a result of environmental influence such as radiation, chemicals and viruses as occurs in carcinogenesis.

The inheritance pattern of genetic abnormalities may be dominant or recessive, autosomal or sex-linked. A dominant gene produces its effects, whether combined with similar dominant or recessive gene. Recessive genes are effective only if both genes are similar. However, when both alleles of a gene pair are expressed in heterozygote state, it is called codominant inheritance. A single gene may express in multiple allelic forms known as polymorphism. Genes on Y-chromosome are determinant for testis and are not known to cause any sex-linked disorder. Therefore, all sex-linked disorders are, in fact, X-linked disorders. All people carrying abnormal gene pairs for a character are affected differently. Penetrance means mathematical expression of mutant gene-character as present in the individual, while variable expressivity is variable expression of mutant gene in the different individuals.

Disoders with multifactorial inheritance. These are disorders which result from the combined effect of genetic composition and environmental influences. Some normal phenotypic characteristics have also multifactorial inheritance, e.g. the colour of hair, eye, skin, height and intelligence. Some examples of disorders where environmental influences unmask the mutant genes are: 1) autosomal recessive inheritance: beta thalassaemia, sickle cell anemia, albinism, Wilson's disease et.al; 2) autosomal codominant inheritance: HLA antigens, blood group antigens; 3) autosomal dominant inheritance: family polyposis coli, hereditary spherocytosis, neurofibromatosis, Marfan's syndrome et.al. 4) sex-(X) linked recessive inheritance: haemophilia A, diabetes insipidus e.al. 5) sex-(X) linked dominant inheritance: hypophosphatacmic rickets, Incontineiitia pignienti et.al.

The causes of acquired damage of cells are various. Their main groups are the following:

1. Reduced oxygen supply (respiratory disease, cardiovascular disease, anemia).
2. Physical agents (mechanical trauma, excessive heat or cold radiations).
3. Chemical agents (these continue to increase enormously with the complexity of industrial processes).
4. Toxins (bacteria, plants, animals e.g. snakes).
5. Viruses.
6. Abnormal immunological reaction (hypersensitivity states, glomerulonephritis).
7. Nutritional deficiencies (vitamin deficiency and malabsorption syndromes).

Cellular reactions to damage depend on the type, duration, and severity of injury induced. The response can range from a minimal and reversible disturbance of cell volume to massive irreversible swelling with a concomitant loss of cell function, followed by death. When injury develops rapidly, it is conventionally referred to as "acute injury." The factor that ultimately determines whether a cell will survive or succumb after injury remains to be unequivocally established. Irreversibility is probably attributable to the effect of the loss of several vital functions coupled with increased degradation of intracellular components. Recent studies indicate that in the early stages of cell injury there are significant losses of phospholipids from cell membranes. This leads to functional alterations of the cell, presumably resulting from activation of intracellular phospholipases.

If stress is sufficiently prolonged, the cells will certainly die; perhaps this occurs when the synthesis of a certain vital molecule or molecules is sufficiently compromised that the renewal of cell substance is critically impaired. In less intense and prolonged forms of stress, termed "chronic injury", cells are able to adapt to environmental abnormalities to the extent that they are capable of augmented rather than diminished function.

Cells may adapt to a pathological (disease) stimulus by extending the three normal physiological adaptive responses: 1. Increased cellular activity - increased functional demand on a tissue can be met by increase in cell number (hyperplasia), as well as by increase in cell size (hypertrophy). 2. Decreased cellular activity - cell atrophy. 3. Alteration of cell morphology (degeneration, apoptosis, necrosis).

The response of cells to an adverse environment is conditioned by numerous intracellular and extracellular factors. These can be classified into four broad categories: extracellular and intracellular milieu, pattern and degree of metabolic activity, level of cell differentiation, and amount, and expression of information contained in the genome.

Studies of acute injury caused by a variety of noxious agents on both isolated cells and tissue have shown a striking similarity in the types and sequence of morphologic changes, regardless of the nature of the injurious agent. The initial event, occurring almost immediately after exposure of a cell to a noxious environment, is a loss of cell volume control, which is rapidly followed by a decrease in the optical density of the cytoplasm because of intracellular swelling (hydropic change) and eventual accumulation of lipid droplets (fatty change). If the noxious agent is particularly toxic, additional alterations are seen: violent movements of the plasma membrane followed by the development of bizarre pseudopodia and blebs of the plasma membrane, nuclear swelling, condensation of nucleus chromatin (pycknosis), dissolution of the nucleus (karyolysis), and finally lysis of the cell (cytolysis).

Cell death is that state in which cells are incapable of any function, including energy generation, homeostatic control, motility, uptake of materials, synthesis, export cell communication and excitability, and reproduction.