NATIONAL OPEN UNIVERSITY OF NIGERIA

COURSE CODE: NSS 203

COURSE TITLE: GENERAL AND CELLULAR PATHOLOGY FOR NURSES

COURSE GUIDE

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INTRODUCTION

NSC 203: General and Cellular Pathology for Nurses is a 200 level 2-unit course, designed in comprehensive modules for all students pursuing the B.Sc program in nursing.

It is purposed to give the basic but explicit description of those general and cellular intricacies of disease process; useful to the modern nursing practitioner. This course guide tells you in brief what the whole course is all about, particular emphasis on important points, personal assessment where pertinent and tutor-marked assignment to enhance your study and to prepare for the in-courses and final examinations. The last module (module 5) is the practical aspect. You will have COMPULSORY sessions of biopsies handling and pots demonstration. Attendance will be taken at these sessions. This shall be supervised by all the teaching staff involved in this course. Regular tutorial classes are also linked to this course. You are advised to attend these sessions.

WHAT YOU WILL LEARN IN THIS COURSE:

The overall aim of this course: NSC 203; General and Cellular Pathology for Nurses, is to enable you to understand the cellular events leading to diseases. From cellular response to stress and noxious substances, to cull injury and death, to wound healing, oedema formation and shock, disorders of cell growth and differentiation down to cancer formation.

COURSE OBJECTIVES:

To achieve the aims set out above, the course sets overall objectives. In addition, each unit also has specific objectives. The unit objectives are always included at the beginning of the unit; you should read them before you start working through the unit. You may want to refer to them during your study of the unit to check on your progress. You should always look at the unit objectives after completing a unit. In this way you can be sure that you have done what was required of you by the unit. Set out below are the wider objectives of the course as a whole. By meeting these objectives, you should have achieved the aims of the course as a whole. On successful completion of the course, you should be able to:

1) Describe cellular responses to stress and noxious stimuli and inflammation.
2) Describe cell injury and cell death.
3) Describe the mechanisms involved in wound healing.
4) Explain the pathology and pathogenesis of oedema and shock.
5) Enumerate and describe the abnormalities of cell growth and differentiation.

WORKING THROUGH THIS COURSE

To run this course successfully, you are required to read the study units, books and other materials provided by the National Open University of Nigeria (NOUN). Each unit contains self-assessment exercises and at the end of the course is a final examination.

The course should run for an average of 12 weeks. Below you will find listed all the components of the course, what you have to do, and how you should allocate your time to each unit in order to complete the course successfully on time.

COURSE MATERIALS

Major components of the course are:
1. The Course Guide
2. Study Units
3. References

STUDY UNITS

The study units in this course are as follows:

The Course Guide:

MODULE 1

Unit 1: Introduction to Pathology
Unit 2: Cellular Responses to Stress and Noxious Stimuli and Inflammation

MODULE 2

Unit 1: Cell Injury and Cell Death I
Unit 2: Cell Injury and Cell Death II
Unit 3: Wound Healing.

MODULE 3

Unit 1: Pathology and Pathogenesis of oedema
Unit 2: Shock: Pathology and Pathogenesis

MODULE 4

Unit 1: Abnormalities of Cell Growth and Differentiation.
Unit 2: Neoplasia.

MODULE 5.

Unit 1: Handling of Biopsies

Unit 2: Pots Demonstration.

Each study unit consists of introduction, specific objectives, reading materials, conclusion, summary, tutor-marked assignments (TMAs), references and further readings. The units direct you to work on exercises related to the required readings. In general, these exercises are on the material you have just covered. Together with tutor-marked assignments, these exercises will assist you in achieving the stated learning objectives of the individual units and of the course.

The Assignment File

The course assignment will cover:

- The definition of cellular pathology and discussion on the various aspects.
- Cellular responses to injury, cellular adaptation, types and description of inflammation with examples.
- Definition of cell injury and cell death, classification of the various causes of cell injury/death, differences between necrosis and apoptosis and the description of the mechanisms of cell injury.
- The mechanisms involved in wound healing.
- The pathology and patho- physiology oedema and shock.
- The description of the abnormalities of cell growth and differentiation and development of cancer.

Assessment

There are two aspects to the assessment of the course. The first are the tutor-marked assignments. Secondly, there is a written examination. In tackling the assignments, you are expected to apply information, knowledge and strategies gathered during the course. The assignments must be submitted to your tutor for formal assessment before the stipulated deadlines. The work you submit to your tutor for assessment will account for 40% of your course mark.

At the end of the course, you will need to sit for a final written examination of two hour duration. This will account for 60% of the total course work.

Tutor-Marked Assignment (TMA)

There are 11 Tutor-marked assignments in the course. You will be given the four (4) to be assessed online. You are advised in your own interest to attempt all the 4 TMA. You will be able to complete the assignments from the information and materials contained in your reading and study units. There is other self activity contained in the instructional material to facilitate your studies. Try to attempt it all. Feel free to consult any of the references to provide you with broader view and a deeper understanding of the course

Final Examination and Grading

The final examination of NSS 203 will be of three hours duration written paper which has a value of 60%. The examination will cover all the units of the course; it is also advisable to consult your reference books for better understanding of the course of study.

Course Marking Scheme

The following table lays out how the actual course marking is broken down.

Assessment	**Marks**
Assignment	4 TMAs of 10 marks each = 40% 0f Course marks
Final Examination	60% of overall course marks
Total	100% of course marks

Course Overview

The table below brings together the units, the number of weeks you should take to complete them, and the assignments that follow them.

Unit	Title of work	Weeks activity	Assessment(End of Unit)
	Course Guide	1	
	MODULE 1		
1	Introduction to Pathology	2	1
2	Cellular Responses to Stress and Noxious Stimuli and Inflammation	3	2
	MODULE 2		
1	Cell Injury and Cell Death I	4	3
2	Cell Injury and Cell Death II	5	4
3	Wound healing	6	5
	MODULE 3		
1	Pathology and Pathogenesis of oedema	7	6
2	Shock: Pathology and Pathogenesis	8	7
	MODULE 4		
1	Abnormalities of Cell Growth and Differentiation	9	8
2	Neoplasia	10	9
	MODULE 5		
1	Handling of Biopsies.	11	10

2	Pots Demonstration	12	11

How to Get the Most from this Course

These study materials have been carefully designed and organized to make this course a lot simplified for you. Think of it as reading the lecture instead of listening to a lecturer. The study units tell you when to read your course material. Just as a lecturer might give you an in-class exercise, your study units provide exercises for you to do at appropriate points.

Each of the study units follows a common format. The first item is an introduction to the subject matter. Next is a set of learning objectives. These objectives let you know what you should be able to do by the time you have completed the unit. When you have finished the unit you must go back and check whether you have achieved the objectives. If you make a habit of doing this, you will significantly improve your chances of passing in flying colors. The main body of the unit has been painstakenly designed with figures, flow-charts, schematic diagrams and tables to make your studying a fulfilling experience.

The following is a practical strategy for working through the course. If you run into any trouble, telephone your tutor. Remember that your tutor's job is to help you; so when you need help, don't hesitate at all to ask your tutor to provide it.

1. Read this **Course Guide** thoroughly.

2. Organize a study schedule. Refer to the "course overview" for more details. Note the time you are expected to spend on each unit and how the assignments relate to the units. Important information, e.g. details of your tutorials, and the date of the first day of the semester, is available. You need to gather all this information in one place, such as your diary or a wall calendar. Whatever method you choose to use, you should decide on and write in your own dates for working on each unit.

3. Once you have created your own study schedule, do everything you can to stick to it. The major reason that students fail is that they get behind with their course work. If you get into difficulty with your schedule, please let your tutor know before it is too late for help.

4. Assemble the study materials. Information about what you need for a unit is given on the contents page at the beginning of each unit. You will almost always need both the study unit you are working on and one of the materials for further reading on your desk at the same time.

5. Work through the unit. The content of the unit itself has been arranged to provide a sequence for you to follow. As you work through the unit you will be instructed to read sections from other sources. Use the unit to guide your reading.

6. Keep in mind that you will learn a lot by doing all your assignments carefully. They have been designed to help you meet the objectives of the course and, therefore will help you pass the exam. Submit all assignments not later than the due date.

7. Review the objectives for each study unit to confirm that you achieved them. If you feel unsure about any of the objectives, review the study materials or consult your tutor.

8. When you are confident that you have achieved a unit's objectives, you can then start on the next unit. Proceed unit by unit through the course and try to pace your study so that you keep yourself on schedule.

9. When you have submitted an assignment to your tutor for marking do not wait for its return before starting on the next unit. Keep to your schedule. When the assignment is returned, pay particular attention to your tutor's comments. Consult your tutor as soon as possible if you have any question or problems.

10. After completing the last unit, review the course and prepare yourself for the final examination. Check that you have achieved the unit objectives. (Listed at the beginning of each unit) and the course objectives (listed in the **Course Guide).**

Facilitators/Tutors and Tutorials

There are 8 hours of tutorials provided in support of this course. You will be notified of the dates, times and location of these tutorials, together with the name and phone numbers of your tutor, as soon as you are allocated a tutorial group. Your tutor will mark and comment on your assignment, keep a close watch on your progress and on any difficulties you might encounter and provide assistance to you during the course. You must mail your tutor-marked assignments to your tutor well before the due date (at least two working days are required). They will be marked by your tutor and returned to you as soon as possible.

Do not hesitate to contact your tutor by telephone, e-mail or discussion board if you need help. Contact your tutor if:

- You do not understand any part of the study units or the assignment
- You have difficulty with the self-tests or exercises
- You have a question or problem with an assignment, with your tutor's comments on an assignment, or with the grading of an assignment.

You should try your best to attend the tutorials. This is the only chance for face to face contact with your tutor and to ask questions which are answered instantly. You can raise any problem you encounter in the course of your study. To gain maximum benefit from course tutorials, prepare a question list before attending them. You will learn a lot from participating and discussing actively.

Best wishes !

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CONTENTS

MODULE 1

UNIT 1: INTRODUCTION TO PATHOLOGY

CONTENTS

1.0. OBJECTIVES:

At the end of this unit, you should be able to:
Define cellular pathology,
Enumerate and discuss the aspects of disease process.

2.0 MAIN CONTENT:

2.1 Definition of Pathology

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.

Elementary biology exposes to the fact that the cell is the unit of life. Two or more cells form a tissue, two or more tissues form an organ and organs, systems. Disease process will therefore be better understood if events at the cellular level are well-understood, hence the term **CELLULAR PATHOLOGY!**

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 practice, and is the scientific foundation for all of medicine.

Traditionally the study of pathology is divided into general pathology and systemic pathology. The former is concerned with the reactions of cells and tissues to abnormal stimuli and to inherited defects, which are the main causes of disease. The latter examines the alterations in specialized organs and tissues that are responsible for disorders that involve these organs

This course will focus on the first division: general pathology.

2.2 Aspects of Pathology

There are four aspects of a disease process that form the core of pathology. These are: its cause *(aetiology)*, the mechanisms of its development *(pathogenesis)*, the biochemical and structural alterations induced in the cells and organs of the body *(molecular and morphologic changes)*, and the functional consequences of these changes *(clinical manifestations)*. For instance, *Plasmodium falciparum* (etiological agent) following mosquito bite, invade the human red cells multiply and undergo development in them (pathogenesis), leading to eventual haemolysis (molecular/morphological changes) and development of anaemia *(clinical manifestations)*.

3.0 CONCLUSION:

Pathology is the link between basic sciences and clinical practice. Disease process is better understood with good foundation in pathology.

4.0 SUMMARY:

This unit teaches that:

- Pathology is the link between basic sciences and clinical practice
- Cellular events precede overt manifestation of disease entity.
- There are four aspect of a disease process forming the core of pathology.

5.0 TUTOR-MARKED ASSIGNMENTS.

a. What is cellular pathology?
b. Discuss the aspects of pathology that you know.

6.0 REFERENCES AND FURTHER READING:

- **Robbins and Cotran Pathologic Basis of Diseases. Eight edition.**
- **Essentials of Pathology. By Emanuel Rubin. Third edition.**

UNIT 2: CELLULAR RESPONSES TO STRESS AND NOXIOUS STIMULI/INFLAMMATION

CONTENTS

1.0 INTRODUCTION.

The normal cell is confined to a fairly narrow range of function and structure by its state of metabolism, differentiation, and specialization; by constraints of neighboring cells; and by the availability of metabolic substrates. It is nevertheless able to handle physiologic demands, maintaining a steady state called *homeostasis.*

2.0 OBJECTIVES.

At the end of this unit, you should be able to:

1 Describe cellular responses to stress and noxious stimuli.
2 Explain cellular adaptation to these stimuli
3 Give an overview of inflammation.
4 Differentiate between acute, chronic and granulomatous inflammation

3.0 MAIN CONTENTS.

3.1 Cellular Responses to Stress and Noxious Stimuli

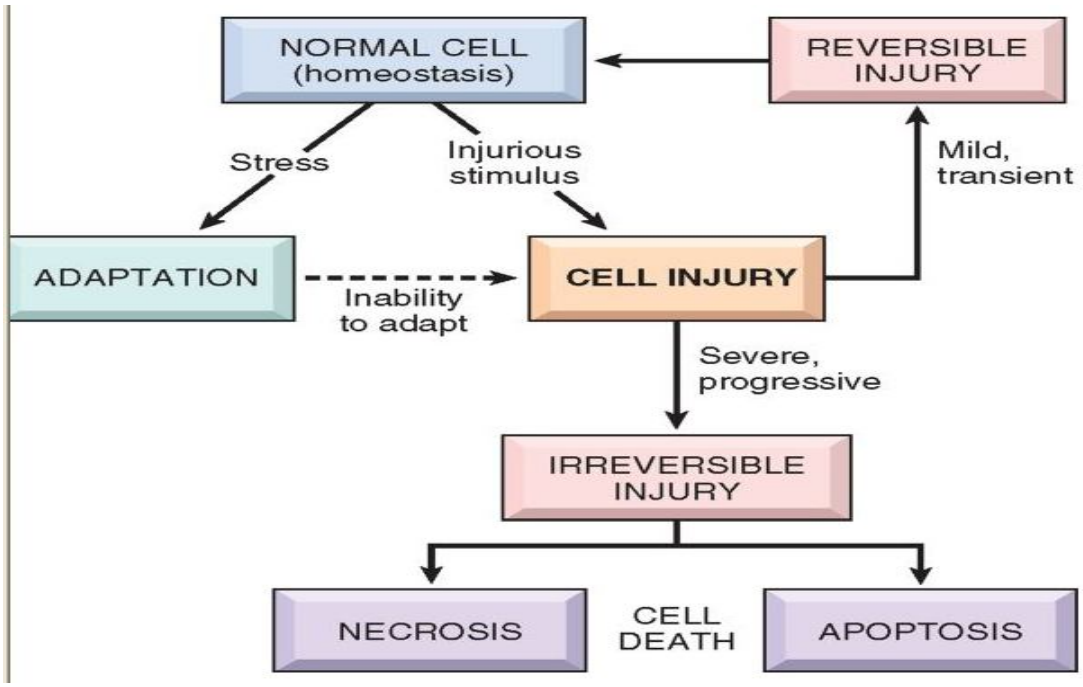


FIGURE 1 *Stages of the cellular response to stress and injurious stimuli.*

TABLE 1 -- Cellular Responses to Injury

Nature of Injurious Stimulus	Cellular Response
ALTERED PHYSIOLOGICAL STIMULI; SOME NONLETHAL INJURIOUS STIMULI	**CELLULAR ADAPTATIONS**
• Increased demand, increased stimulation (e.g., by growth factors, hormones) • Decreased nutrients, decreased stimulation • Chronic irritation (physical or chemical)	• Hyperplasia, hypertrophy • Atrophy • Metaplasia
REDUCED OXYGEN SUPPLY; CHEMICAL INJURY; MICROBIAL INFECTION	**CELL INJURY**
• Acute and transient • Progressive and severe (including DNA damage)	• Acute reversible injury Cellular swelling fatty change • Irreversible injury → cell death Necrosis Apoptosis
METABOLIC ALTERATIONS, GENETIC OR ACQUIRED; CHRONIC INJURY	**INTRACELLULAR ACCUMULATIONS; CALCIFICATION**
CUMULATIVE SUBLETHAL INJURY OVER LONG LIFE SPAN	**CELLULAR AGING**

Adaptations: These are reversible functional and structural responses to more severe physiologic stresses and some pathologic stimuli, during which new but altered steady states are achieved, allowing the cell to survive and continue to function (Fig. 1 and Table 1). The adaptive response may consist of an increase in the size of cells (hypertrophy) and functional activity, an increase in their number (hyperplasia), a decrease in the size and metabolic activity of cells (atrophy), or a change in the phenotype of cells (metaplasia). When the stress is eliminated the cell can recover to its original state without having suffered any harmful consequences.

If the limits of adaptive responses are exceeded or if cells are exposed to injurious agents or stress, deprived of essential nutrients, or become compromised by mutations that affect essential cellular constituents, a sequence of events follows that is termed *cell injury* (see Fig. 1). Cell injury is *reversible* up to a certain point, but if the stimulus persists or is severe enough from the beginning, the cell suffers *irreversible injury* and ultimately *cell death*. *Adaptation, reversible injury*, and *cell death* may be stages of progressive impairment following different types of insults. For instance, in response to increased hemodynamic loads, the heart muscle becomes enlarged, a form of adaptation, and can even undergo injury. If the blood supply to the myocardium is compromised or inadequate, the muscle first suffers reversible injury, manifested by certain cytoplasmic changes. Eventually, the cells suffer irreversible injury and die.

3.2 Inflammation.

The ability to get rid of damaged or necrotic tissues and foreign invaders, such as microbes is essential to the survival of organisms. The host response that accomplishes these goals is called *inflammation. It is fundamentally a protective response*, designed to rid the organism of both the initial cause of cell injury (e.g., microbes, toxins) and the consequences of such injury (e.g., necrotic cells and tissues).

Without inflammation infections would go unchecked, wounds would never heal, and injured tissues might remain permanent festering sores. In the practice of medicine the importance of inflammation is that it can sometimes be inappropriately triggered or poorly controlled, and is thus the cause of tissue injury in many disorders.

Inflammation is a complex reaction in tissues that consists mainly of responses of blood vessels and leukocytes. These vascular and cellular reactions of inflammation are triggered by soluble factors that are produced by various cells or derived from plasma proteins and are generated or activated in response to the inflammatory stimulus.

Types:

Inflammation may be **acute** or **chronic**. This is dependent on 1) the nature of the stimulus and 2) the effectiveness of the initial reaction in eliminating the stimulus or the damaged tissues.

Acute inflammation 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). When acute inflammation is successful in eliminating the offenders the reaction subsides, but if the response fails to clear the invaders it can progress to a chronic phase.

Chronic inflammation may follow acute inflammation or be insidious in onset. It is of longer duration and is associated with the presence of lymphocytes and macrophages, the proliferation of blood vessels, fibrosis, and tissue destruction

Some historical highlights:

Although clinical features of inflammation were described in an Egyptian papyrus dated around 3000 BC, Celsus, a Roman writer of the first century AD, first listed the four cardinal signs of inflammation: *rubor* (redness), *tumor* (swelling), *calor* (heat), and *dolor* (pain).[1] These signs are typically more prominent in acute inflammation than in chronic inflammation. A fifth clinical sign, loss of function *(functio laesa)*, was added by Rudolf Virchow in the 19th century

3.2.1 Acute inflammation

Acute is a rapid host response that serves to deliver leukocytes and plasma proteins, such as antibodies, to sites of infection or tissue injury. 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.

Stimulus for Acute Inflammation.

Infections (bacterial, viral, fungal, parasitic) and microbial toxins are among the most common and medically important causes of inflammation.

Tissue necrosis from any cause, including *ischemia* (as in a myocardial infarct), *trauma*, and *physical and chemical injury* (e.g., thermal injury, as in burns or frostbite; irradiation; exposure to some environmental chemicals).

Foreign bodies (splinters, dirt, sutures) typically elicit inflammation because they cause traumatic tissue injury or carry microbes.

Immune reactions (also called hypersensitivity reactions) are reactions in which the normally protective immune system damages the individual's own tissues. The injurious immune responses may be directed against self antigens, causing *autoimmune diseases*, or may be excessive reactions against environmental substances or microbes

All inflammatory reactions share the same basic features, although different stimuli may induce reactions with some distinctive characteristics.

A hallmark of acute inflammation is increased vascular permeability leading to the escape of a protein-rich exudate into the extravascular tissue, causing *edema*. Several mechanisms are responsible for the increased vascular permeability.

Reactions of Blood Vessels in Acute Inflammation:

In inflammation, blood vessels undergo a series of changes that are designed to maximize the movement of plasma proteins and circulating cells out of the circulation and into the site of infection or injury. The escape of fluid, proteins, and blood cells from the vascular system into the interstitial tissue or body cavities is known as *exudation*. 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. In contrast, a *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. *Edema* denotes an excess of fluid in the interstitial tissue or serous cavities; it can be either an exudate or a transudate. *Pus*, a *purulent* exudate, is an inflammatory exudate rich in leukocytes (mostly neutrophils), the debris of dead cells and, in many cases, microbes.

Reactions of Leukocytes in Inflammation.

A critical function of inflammation is to deliver leukocytes to the site of injury and to activate the leukocytes to eliminate the offending agents. The most important leukocytes in typical inflammatory reactions are the ones capable of phagocytosis, namely neutrophils and macrophages.

Outcomes of Acute Inflammation. 1) Complete resolution,

2) Healing by connective tissue replacement (fibrosis) or

3) Progression of the response to chronic inflammation.

3.2.2. Chronic Inflammation

Chronic inflammation is inflammation of prolonged duration (weeks or months) in which inflammation, tissue injury, and attempts at repair coexist, in varying combinations. It may follow acute inflammation, as described earlier, or chronic inflammation may begin insidiously, as a low-grade, smoldering response without any manifestations of an acute reaction. This latter type of chronic inflammation is the cause of tissue damage in some of the most common and disabling human diseases, such as rheumatoid arthritis, atherosclerosis, tuberculosis, and pulmonary fibrosis. It has also been implicated in the progression of cancer and in diseases once thought to be purely degenerative, such as Alzheimer disease.

Causes:

- *Persistent infections* by microorganisms that is difficult to eradicate, such as mycobacteria, and certain viruses, fungi, and parasites.
- *Immune-mediated inflammatory diseases*.
- *Prolonged exposure to potentially toxic agents, either exogenous (e.g. silicosis) or endogenous(e.g. atherosclerosis).*

Morphologic Features: In contrast to acute inflammation, which is manifested by vascular changes, edema, and predominantly neutrophilic infiltration, *chronic inflammation is characterized by:*

- *Infiltration with mononuclear cells*, which include macrophages, lymphocytes, plasma cells, eosinophils and mast cells. The predominant cellular components are the macrophages.
- *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.*

3.2.3 Granulomatous Inflammation: *Granulomatous inflammation is a distinctive pattern of chronic inflammation* that is encountered in a limited number of infectious and some noninfectious conditions.

***A granuloma is a focus of chronic inflammation consisting of a microscopic aggregation of macrophages that are transformed into epithelium-like cells, surrounded by a collar of mononuclear leukocytes, principally lymphocytes and occasionally plasma cells*.**

TABLE 2 -- Examples of Diseases with Granulomatous Inflammation

Disease	Cause	Tissue Reaction
Tuberculosis	*Mycobacterium tuberculosis*	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	*Mycobacterium leprae*	Acid-fast bacilli in macrophages; noncaseating granulomas
Syphilis	*Treponema pallidum*	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

3.2.4 Systemic Effects of Inflammation.

The systemic changes associated with acute inflammation are collectively called the *acute-phase response*, or the systemic inflammatory response syndrome. These changes are reactions to cytokines whose production is stimulated by bacterial products such as lipopolysaccharide (LPS) and by other inflammatory stimuli. The acute-phase response consists of several clinical and pathologic changes:

1) *Fever*, characterized by an elevation of body temperature, usually by 1° to 4°C, is one of the most prominent manifestations of the acute-phase response, especially when

inflammation is associated with infection. Fever is produced in response to substances called *pyrogens* that act by stimulating prostaglandin synthesis in the vascular and perivascular cells of the hypothalamus.

2) *Acute-phase proteins* are plasma proteins, mostly synthesized in the liver, whose plasma concentrations may increase several hundred-fold as part of the response to inflammatory stimuli.
3) *Leukocytosis* 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 /μL, but sometimes it may reach extraordinarily high levels of 40,000 to 100,000 cells/μL. These extreme elevations are referred to as *leukemoid reactions*, because they are similar to the white cell counts observed in leukemia and have to be distinguished from leukemia.
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) High levels of cytokines cause various clinical manifestations such as disseminated intravascular coagulation, cardiovascular failure, and metabolic disturbance, which are described as *septic shock.*

CONCLUSION. The response of the cell to stress and noxious stimuli, its adaptation to those stimuli and ignition of inflammatory response when cellular adaptation is overwhelmed form the bedrock of disease pathogenesis. The understanding of this foundation of pathology is indispensable!

SUMMARY.

This unit teaches that:

1) Disease process commences at the cellular level following the effect of stress and noxious stimuli.
2) Cellular adaptation is necessary to limit progression of the disease. Otherwise, inflammatory process begins.
3) Inflammatory response can be acute or chronic.

TUTOR-MARKED ASSIGNMENT.

a. **Enumerate cellular responses to injury.**
b. **What is cellular adaptation?**
c. **What are the types of inflammation that we have?**
d. **What are the components of acute and chronic inflammation? Give examples.**
e. **Briefly describe granulomatous inflammation.**

REFERENCES AND FURTHER READING:

- **Robbins and Cotran Pathologic Basis of Diseases. Eight edition.**
- **Essentials of Pathology. By Emanuel Rubin. Third edition.**

MODULE 2.

UNIT 1: CELL INJURY AND CELL DEATH I

CONTENTS

1.0 INTRODUCTION

As earlier mentioned, cell injury results when cells are stressed so severely that they are no longer able to adapt or when cells are exposed to inherently damaging agents or suffer from intrinsic abnormalities. Injury may progress through a reversible stage and culminate in cell death (see Fig. 1).

2.0 OBJECTIVES. At the end of this unit, you should be able to:

2.1 Describe cell injury and cell death
2.2 Classify and enumerate the causes of cell injury.
2.3 Enumerate the morphologic alterations observed following cell injury.
2.4 Describe the mechanisms of cell injury.

3.0 MAIN CONTENTS:

3.1 Cell Injury and Cell Death

Reversible cell injury. In early stages or mild forms of injury, the functional and morphologic changes are reversible if the damaging stimulus is removed. The hallmarks of

reversible injury are reduced oxidative phosphorylation with resultant depletion of energy stores in the form of adenosine triphosphate (ATP), and cellular swelling caused by changes in ion concentrations and water influx. In addition, various intracellular organelles, such as mitochondria and the cytoskeleton, may also show alterations.

Cell death. With continuing damage the injury becomes irreversible, at which time the cell cannot recover and it dies. *There are two principal types of cell death, necrosis and apoptosis, which differ in their morphology, mechanisms, and roles in physiology and disease.*

When damage to membranes is severe, lysosomal enzymes enter the cytoplasm and digest the cell, and cellular contents leak out, resulting in *necrosis*. In situations when the cell's DNA or proteins are damaged beyond repair, the cell kills itself by *apoptosis*, a form of cell death that is characterized by nuclear dissolution, fragmentation of the cell without complete loss of membrane integrity, and rapid removal of the cellular debris.

Whereas necrosis is always a pathologic process, apoptosis serves many normal functions and is not necessarily associated with cell injury. Cell death is also sometimes the end result of *autophagy*. Although it is easier to understand these pathways of cell death by discussing them separately, there may be many connections between them. Both apoptosis and necrosis may be seen in response to the same insult, such as ischemia, perhaps at different stages. Apoptosis can progress to necrosis, and cell death during autophagy may show many of the biochemical characteristics of apoptosis.

3.2 Causes of Cell Injury.

The causes of cell injury range from the external gross physical violence of an automobile accident to subtle internal abnormalities, such as a genetic mutation causing lack of a vital enzyme that impairs normal metabolic function. Most injurious stimuli can be grouped into the following broad categories.

- **Oxygen Deprivation.**
- **Physical Agents.**
- **Chemical Agents and Drugs.**
- **Infectious Agents.**
- **Immunologic Reactions.**
- **Genetic Derangements.**
- **Nutritional Imbalances.**

Oxygen Deprivation. Hypo*xia* is a deficiency of oxygen, which causes cell injury by reducing aerobic oxidative respiration. Hypoxia is an extremely important and common cause of cell injury and cell death. *Causes of hypoxia* include reduced blood flow (celled *ischemia*), inadequate oxygenation of the blood due to cardio-respiratory failure, and decreased oxygen-carrying capacity of the blood, as in anemia or carbon monoxide

poisoning (producing a stable carbon monoxy-hemoglobin that blocks oxygen carriage) or after severe blood loss. Depending on the severity of the hypoxic state, cells may adapt, undergo injury, or die. For example, if an artery is narrowed, the tissue supplied by that vessel may initially shrink in size (atrophy), whereas more severe or sudden hypoxia induces injury and cell death.

Physical Agents. Physical agents capable of causing cell injury include mechanical trauma, extremes of temperature (burns and deep cold), sudden changes in atmospheric pressure, radiation, and electric shock.

Chemical Agents and Drugs. The list of chemicals that may produce cell injury defies compilation. Simple chemicals such as glucose or salt in hypertonic concentrations may cause cell injury directly or by deranging electrolyte balance in cells. Even oxygen at high concentrations is toxic. Trace amounts of *poisons*, such as arsenic, cyanide, or mercuric salts, may destroy sufficient numbers of cells within minutes or hours to cause death. Other potentially injurious substances are our daily companions: environmental and air pollutants, insecticides, and herbicides; industrial and occupational hazards, such as carbon monoxide and asbestos; recreational drugs such as alcohol; and the ever-increasing variety of therapeutic drugs.

Infectious Agents. These agents range from the submicroscopic viruses to the large tapeworms. In between are the rickettsiae, bacteria, fungi, and higher forms of parasites.

Immunologic Reactions. The immune system serves an essential function in defense against infectious pathogens, but immune reactions may also cause cell injury. Injurious reactions to endogenous self-antigens are responsible for several autoimmune diseases.

Genetic Derangements. Genetic abnormalities may result in a defect as severe as the congenital malformations associated with Down syndrome, caused by a chromosomal anomaly, or as subtle as the decreased life span of red blood cells caused by a single amino acid substitution in hemoglobin in sickle cell anemia. Genetic defects may cause cell injury because of deficiency of functional proteins, such as enzyme defects in inborn errors of metabolism, or accumulation of damaged DNA or misfolded proteins, both of which trigger cell death when they are beyond repair. Variations in the genetic makeup can also influence the susceptibility of cells to injury by chemicals and other environmental insults.

Nutritional Imbalances. Nutritional imbalances continue to be major causes of cell injury. Protein-calorie deficiencies cause an appalling number of deaths, chiefly among underprivileged populations. Deficiencies of specific vitamins are found throughout the world. Nutritional problems can be self-imposed, as in anorexia nervosa (self-induced starvation). Ironically, nutritional excesses have also become important causes of cell injury. Excess of cholesterol predisposes to atherosclerosis; obesity is associated with

increased incidence of several important diseases, such as diabetes and cancer. Atherosclerosis is virtually endemic in the United States, and obesity is rampant. In addition to the problems of under nutrition and over nutrition, the composition of the diet makes a significant contribution to a number of diseases.

3.3 Morphologic Alterations in Cell Injury.

All stresses and noxious influences exert their effects first at the molecular or biochemical level. There is a time lag between the stress and the morphologic changes of cell injury or death; the duration of this delay may vary with the sensitivity of the methods used to detect these changes.

With histochemical or ultra structural techniques, changes may be seen in minutes to hours after injury; however, it may take considerably longer (hours to days) before changes can be seen by light microscopy or on gross examination.

As would be expected, the morphologic manifestations of necrosis take more time to develop than those of reversible damage. For example, in ischemia of the myocardium, cell swelling is a reversible morphologic change that may occur in a matter of minutes, and may progress to irreversibility within an hour or two. Unmistakable light microscopic changes of cell death, however, may not be seen until 4 to 12 hours after total ischemia.

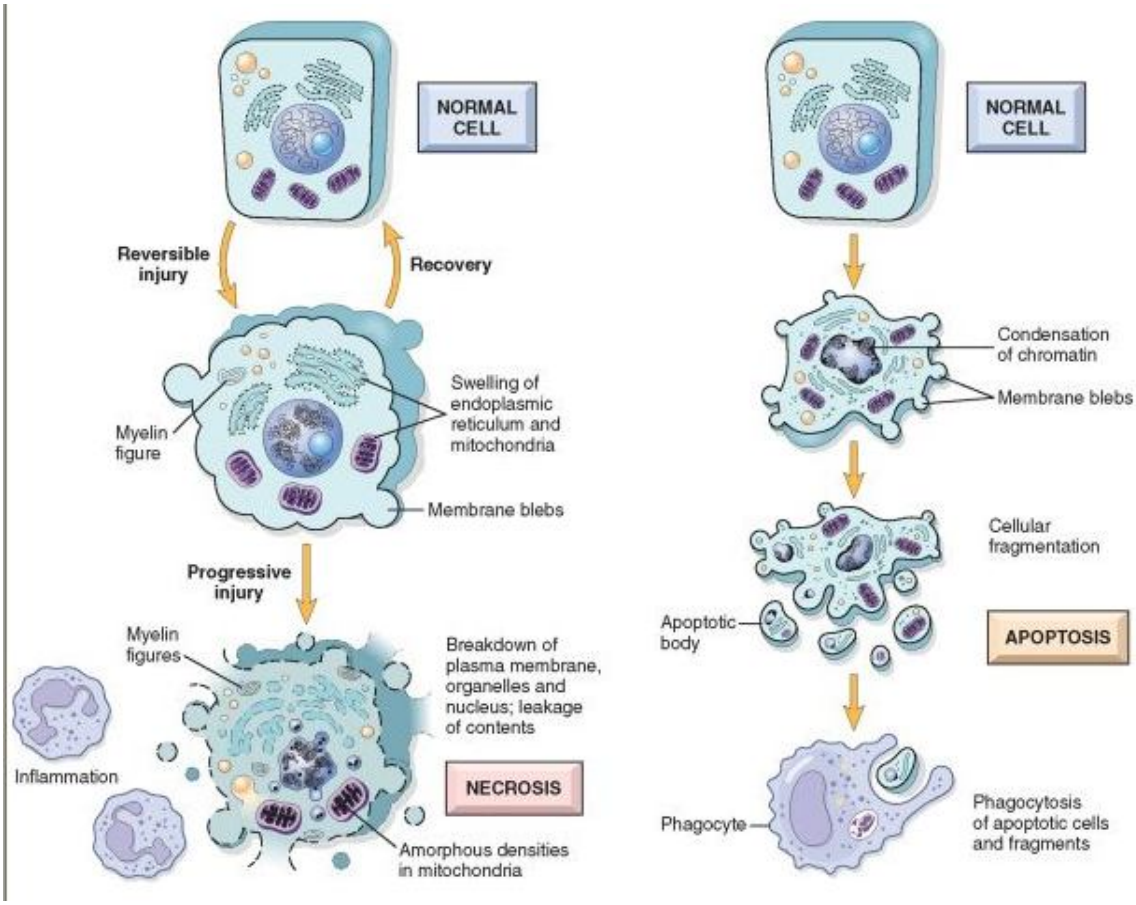


FIGURE 2 *Schematic illustration of the morphologic changes in cell injury culminating in necrosis or apoptosis.*

TABLE 3 -- Features of Necrosis and Apoptosis

Feature	Necrosis	Apoptosis
Cell size	Enlarged (swelling)	Reduced (shrinkage)
Nucleus	Pyknosis → karyorrhexis → karyolysis	Fragmentation into nucleosome-size fragments
Plasma membrane	Disrupted	Intact; altered structure, especially orientation of lipids
Cellular contents	Enzymatic digestion; may leak out of cell	Intact; may be released in apoptotic bodies
Adjacent inflammation	Frequent	No
Physiologic or pathologic role	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

Reversible injury: Two features of reversible cell injury can be recognized under the light microscope: *cellular swelling* and *fatty change*.

Cellular swelling appears whenever cells are incapable of maintaining ionic and fluid homeostasis and is the result of failure of energy-dependent ion pumps in the plasma membrane.

Fatty change occurs in hypoxic, toxic or metabolic injuries. It is manifested by the appearance of lipid vacuoles in the cytoplasm and seen mainly in cells involved in and dependent on fat metabolism, such as hepatocytes and myocardial cells.

NECROSIS:

The morphologic appearance of necrosis is the result of *denaturation of intracellular proteins and enzymatic digestion of the lethally injured cell* (cells placed immediately in fixative are dead but not necrotic)

Patterns of tissue necrosis:

- **Coagulative necrosis** is a form of necrosis in which the architecture of dead tissues is preserved for a span of at least some days
- **Liquefactive necrosis**, in contrast to coagulative necrosis, 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
- **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.
- **Caseous necrosis** is encountered most often in foci of tuberculous infection. The term “caseous” (cheeselike) is derived from the friable white appearance of the area of necrosis. On microscopic examination, 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**.
- **Fat necrosis** is a term that is well fixed in medical parlance but does not in reality denote a specific pattern of necrosis. Rather, 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.
- **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.

Ultimately, in the living patient most necrotic cells and their contents disappear by phagocytosis of the debris and enzymatic digestion by leukocytes. If necrotic cells and cellular debris are not promptly destroyed and reabsorbed, they tend to attract calcium

salts and other minerals and to become calcified. This phenomenon is called ***dystrophic calcification***

3.4 Mechanisms of Cell Injury.

The discussion of the cellular pathology of cell injury and necrosis sets the stage for a consideration of the mechanisms and biochemical pathways of cell injury. The mechanisms responsible for cell injury are complex. There are, however, several principles that are relevant to most forms of cell injury.

Principles:

- *The cellular response to injurious stimuli depends on the nature of the injury, its duration, and its severity.*
- *The consequences of cell injury depend on the type, state, and adaptability of the injured cell*
- *Cell injury results from different biochemical mechanisms acting on several essential cellular components*

Any injurious stimulus may simultaneously trigger multiple interconnected mechanisms that damage cells. This is one reason why it is difficult to ascribe cell injury in a particular situation to a single or even dominant biochemical derangement.

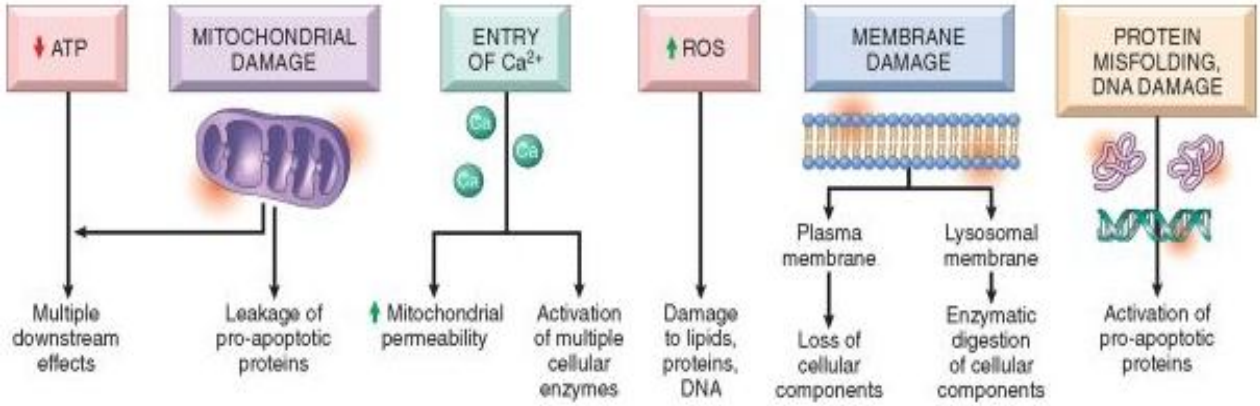


FIGURE 3: *The principal mechanisms of cell injury, and their biochemical and functional effects, are shown. These are described in detail in the text.*

3.4.1 Depletion of ATP:

ATP depletion and decreased ATP synthesis are frequently associated with both hypoxic and chemical (toxic) injury. The major causes of ATP depletion are reduced supply of oxygen and nutrients, mitochondrial damage, and the actions of some toxins (e.g., cyanide).

ATP is produced in two ways. The major pathway in mammalian cells is oxidative phosphorylation of adenosine diphosphate, in a reaction that results in reduction of oxygen by the electron transfer system of mitochondria. The second is the glycolytic pathway, which can generate ATP in the absence of oxygen using glucose derived either from body fluids or from the hydrolysis of glycogen.

3.4.2 Mitochondrial Damage.

Mitochondria are the cell's suppliers of life-sustaining energy in the form of ATP, but they are also critical players in cell injury and death. Mitochondria can be damaged by increases of cytosolic Ca^{2+}, reactive oxygen species (discussed below), and oxygen deprivation, and so they are sensitive to virtually all types of injurious stimuli, including hypoxia and toxins. In addition, mutations in mitochondrial genes are the cause of some inherited diseases.

There are two major *consequences of mitochondrial damage*: 1) Formation of a high-conductance channel in the mitochondrial membrane, called the *mitochondrial permeability transition pore. 2)* The mitochondria also sequester between their outer and inner membranes several proteins that are capable of activating apoptotic pathways; these include cytochrome *c* and proteins that indirectly activate apoptosis inducing enzymes called caspases. Increased permeability of the outer mitochondrial membrane may result in leakage of these proteins into the cytosol, and death by apoptosis.

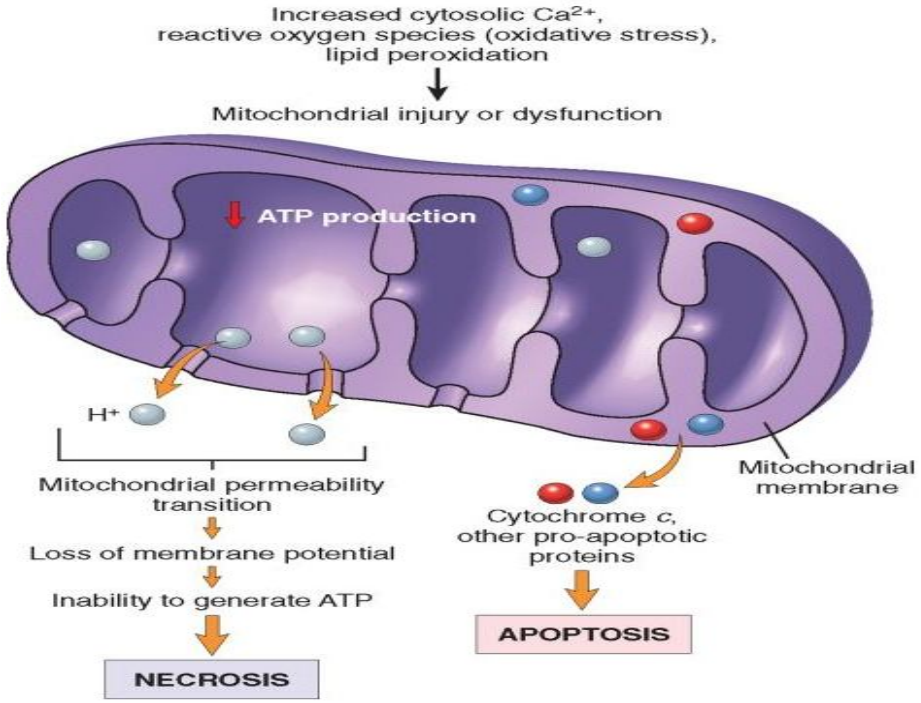


FIGURE 4 *Consequences of mitochondrial dysfunction, culminating in cell death by necrosis or apoptosis.*

3.4.3 Influx of Calcium and Loss of Calcium Homeostasis. The finding that depleting calcium protects cells from injury induced by a variety of harmful stimuli indicates that calcium ions are important mediators of cell injury.

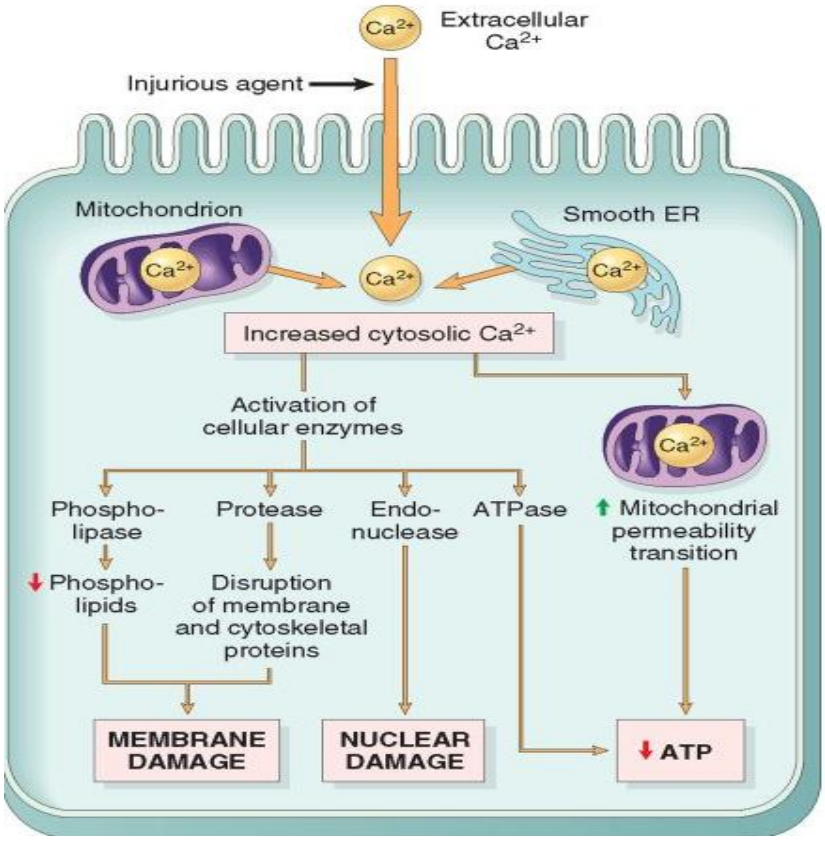


FIGURE 5 *The role of increased cytosolic calcium in cell injury. ER, endoplasmic reticulum.*

Increased intracellular Ca^{2+} causes cell injury by several mechanisms:

- The accumulation of Ca^{2+} in mitochondria results in opening of the mitochondrial permeability transition pore and, as described above, failure of ATP generation.
- Increased cytosolic Ca^{2+} activates a number of enzymes, with potentially deleterious cellular effects. These enzymes include *phospholipases* (which cause membrane damage), *proteases* (which break down both membrane and cytoskeletal proteins), *endonucleases* (which are responsible for DNA and chromatin fragmentation), and *ATPases* (thereby hastening ATP depletion).
- Increased intracellular Ca^{2+} levels also result in the induction of apoptosis, by direct activation of caspases and by increasing mitochondrial permeability.

3.4.4 Accumulation of Oxygen-derived Free Radicals (oxidative stress).

Cell injury induced by free radicals, particularly reactive oxygen species, is an important mechanism of cell damage in many pathologic conditions, such as chemical and radiation injury, ischemia-reperfusion injury (induced by restoration of blood flow in ischemic tissue), cellular aging, and microbial killing by phagocytes.

Free radicals are chemical species that have a single unpaired electron in an outer orbit. Energy created by this unstable configuration is released through reactions with adjacent molecules, such as inorganic or organic chemicals—proteins, lipids, carbohydrates, nucleic acids—many of which are key components of cell membranes and nuclei.

Table 4. Properties of the Principal Free Radicals Involved in Cell Injury

Properties	O_2^-	H_2O_2	$^{\cdot}OH$	$ONOO^-$
MECHANISMS OF PRODUCTION	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 NO synthase in many cell types (endothelial cells, leukocytes, neurons, others)
MECHANISMS OF INACTIVATION	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)
PATHOLOGIC EFFECTS	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; $ONOO^{-}$, peroxynitrite; ROS, reactive oxygen species; SOD, superoxide dismutase.

Pathologic Effects of Free Radicals:

- *Lipid peroxidation in membranes*
- *Oxidative modification of proteins*
- *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.

3.4.5 Defects in Membrane Permeability.

Early loss of selective membrane permeability leading ultimately to overt membrane damage is a consistent feature of most forms of cell injury (except apoptosis).

Mechanisms of Membrane Damage:

- *Reactive oxygen species*
- *Decreased phospholipids synthesis*
- *Increased phospholipids breakdown.*
- *Cytoskeletal abnormalities*

3.4.6 Damage to DNA and Proteins.

Cells have mechanisms that repair damage to DNA, but if this damage is too severe to be corrected (e.g., after exposure to DNA damaging drugs, radiation, or oxidative stress), the cell initiates a suicide program that results in death by apoptosis. A similar reaction is triggered by improperly folded proteins, which may be the result of inherited mutations or external triggers such as free radicals. However, the molecular mechanisms connecting most forms of cell injury to ultimate cell death have proved elusive, for several reasons. The "point of no return," at which the damage becomes irreversible, is still largely undefined, and there are no reliable morphologic or biochemical correlates of irreversibility. *Two phenomena consistently characterize irreversibility—the inability to reverse mitochondrial dysfunction* (lack of oxidative phosphorylation and ATP generation) even after resolution of the original injury, and *profound disturbances in membrane function*. As mentioned earlier, injury to lysosomal membranes results in the enzymatic dissolution of the injured cell that is characteristic of necrosis.

4.0 CONCLUSION.

The knowledge of the various classes and types of cell injury and cell death, the morphologic patterns involved and the mechanism by which these agents and events bring about irreversible injuries forms the bedrock of development of antidotes to counteract their effects. Hence a good understanding of the pathways is an essential tool for modern nursing practice.

5.0 SUMMARY.

This unit teaches us about:

Cell injury and cell death.
The classification and examples of the causes of cell injury.
The morphologic pattern of cell injuries and
The mechanisms by which the injuries bring about irreversible cell death.

6.0 TUTOR-MARKED ASSIGNMENT.

- Define cell injury and cell death.
- Classify and enumerate the various causes of cell injury/death.
- Differentiate between necrosis and apoptosis.
- Enumerate the mechanisms of cell injury and briefly describe one of them.
- What are free radicals? Give examples**.**

UNIT 2: CELL INJURY AND CELL DEATH II

CONTENTS

1.0 INTRODUCTION

With a knowledge base of the causes, morphology, and mechanisms of cell injury and necrotic cell death, it will be pertinent to now describe some common and clinically significant forms of cell injury that typically culminate in necrosis.

2.0 OBJECTIVES. At the end of this unit, you should be able to:

Describe selected examples of cell injury and necrosis.
Differentiate between apoptosis and autophagy.
Describe intracellular accumulations and pathologic calcification
Explain cellular aging.

3.0 MAIN CONTENT:

3.1 Clinico-Pathologic Correlations: Selected Examples of Cell Injury and Necrosis.

3.1.1 Ischemic and Hypoxic Injury: This is the most common type of cell injury in clinical medicine and has been studied extensively in humans, in experimental animals, and in culture systems. Hypoxia, referring to reduced oxygen availability, may occur in a variety of clinical settings, described earlier. In ischemia, on the other hand, the supply of oxygen and nutrients is decreased most often because of reduced blood flow as a consequence of a mechanical obstruction in the arterial system. It can also be caused by reduced venous drainage. In contrast to hypoxia, during which energy production by anaerobic glycolysis can continue, ischemia compromises the delivery of substrates for glycolysis. Thus, in ischemic tissues, not only is aerobic metabolism compromised but anaerobic energy generation also stops after glycolytic substrates are exhausted, or glycolysis is inhibited by the accumulation of metabolites that would have been removed otherwise by blood flow. For this reason,
Ischemia tends to cause more rapid and severe cell and tissue injury than does hypoxia in the absence of ischemia. If ischemia persists, irreversible injury and necrosis ensue.

3.1.2 Ischemia-reperfusion Injury: Restoration of blood flow to ischemic tissues can promote recovery of cells if they are reversibly injured. However, under certain circumstances, when blood flow is restored to cells that have been ischemic but have not died, injury is paradoxically exacerbated and proceeds at an accelerated pace. 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.

3.1.3 Chemical (toxic) Injury: Chemical injury remains a frequent problem in clinical medicine and is a major limitation to drug therapy. Because many drugs are metabolized in the liver, this organ

is a frequent target of drug toxicity. In fact, toxic liver injury is perhaps the most frequent reason for terminating the therapeutic use or development of a drug.

Chemicals induce cell injury by one of two general mechanisms:

1) Some chemicals can injure cells *directly* by combining with critical molecular components. For example, in mercuric chloride poisoning, mercury binds to the sulfhydryl groups of cell membrane proteins, causing increased membrane permeability and inhibition of ion transport.
2) Most toxic chemicals are not biologically active in their native form but must be converted to reactive toxic metabolites, which then act on target molecules. This modification is usually accomplished by the cytochrome P-450 mixed-function oxidases in the smooth ER of the liver and other organs.

3.2 Apoptosis/Autophagy

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. Apoptotic cells break up into fragments, called apoptotic bodies, which contain portions of the cytoplasm and nucleus. The plasma membrane of the apoptotic cell and bodies remains intact, but its structure is altered in such a way that these become “tasty” targets for phagocytes. The dead cell and its fragments are rapidly devoured, before the contents have leaked out, and therefore cell death by this pathway does not elicit an inflammatory reaction in the host. The process was recognized in 1972 by the distinctive morphologic appearance of membrane-bound fragments derived from cells, and named after the Greek designation for “falling off”. It was quickly appreciated that apoptosis was a unique mechanism of cell death, distinct from necrosis, which is characterized by loss of membrane integrity, enzymatic digestion of cells, leakage of cellular contents, and frequently a host reaction. However, apoptosis and necrosis sometimes coexist, and apoptosis induced by some pathologic stimuli may progress to necrosis.

Causes: Occurs normally both during development and throughout adulthood, and serves to eliminate unwanted, aged or potentially harmful cells. It is also a pathologic event when diseased cells become damaged beyond repair and are eliminated.

Autophagy is a process in which a cell eats its own contents. It is a survival mechanism in times of nutrient deprivation, when the starved cell lives by cannibalizing itself and recycling the digested contents. In this process intracellular organelles and portions of cytosol are first sequestered from the cytoplasm in an *autophagic vacuole*, which subsequently fuses with lysosomes to form an *autophagolysosome*, and the cellular

components are digested by lysosomal enzymes. Nevertheless, autophagy has been invoked as a mechanism of cell loss in various diseases, including degenerative diseases of the nervous system and muscle; in many of these disorders, the damaged cells contain abundant autophagic vacuoles.

3.3 Intracellular Accumulations

One of the manifestations of metabolic derangements in cells is the intracellular accumulation of abnormal amounts of various substances. The stockpiled substances fall into two categories:

(1) a *normal cellular constituent*, such as water, lipids, proteins, and carbohydrates, that accumulates in excess; or

(2) an *abnormal substance*, either exogenous, such as a mineral or products of infectious agents, or endogenous, such as a product of abnormal synthesis or metabolism. These substances may accumulate either transiently or permanently, and they may be harmless to the cells, but on occasion they are severely toxic. The substance may be located in either the cytoplasm (frequently within phagolysosomes) or the nucleus. In some instances the cell may be producing the abnormal substance, and in others it may be merely storing products of pathologic processes occurring elsewhere in the body.

Most accumulations are attributable to four types of abnormalities:

- Normal endogenous substance is produced at a normal or increased rate, but the rate of metabolism is inadequate to remove it. Example: fatty change in the liver and reabsorption protein droplets in the tubules of the kidneys.
- An abnormal endogenous substance, typically the product of a mutated gene, accumulates because of defects in protein folding and transport and an inability to degrade the abnormal protein efficiently. Example: accumulation of mutated α1-antitrypsin in liver cells.
- Normal endogenous substance accumulates because of defects, usually inherited, in enzymes that are required for the metabolism of the substance. Examples include diseases caused by genetic defects in enzymes involved in the metabolism of lipid and carbohydrates, resulting in intracellular deposition of these substances, largely in lysosomes.
- An abnormal exogenous substance is deposited and accumulates because the cell has neither the enzymatic machinery to degrade the substance nor the ability to transport it to other sites. Accumulations of carbon particles and nonmetabolizable chemicals such as silica are examples of this type of alteration.

Pathologic Calcification.

Pathologic calcification is the abnormal tissue deposition of calcium salts, together with smaller amounts of iron, magnesium, and other mineral salts. There are two forms of pathologic calcification. When the deposition occurs locally in dying tissues it is known as *dystrophic calcification*; it occurs despite normal serum levels of calcium and in the absence of derangements in calcium metabolism. In contrast, the deposition of calcium salts in otherwise normal tissues is known as *metastatic calcification*, and it almost always results from hypercalcemia secondary to some disturbance in calcium metabolism.

a) **Dystrophic calcification.** Dystrophic calcification is encountered in areas of necrosis, whether they are of coagulative, caseous, or Liquefactive type, and in foci of enzymatic necrosis of fat. Calcification is almost always present in the atheromas of advanced atherosclerosis. It also commonly develops in aging or damaged heart valves, further hampering their function, whatever the site of deposition, 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.

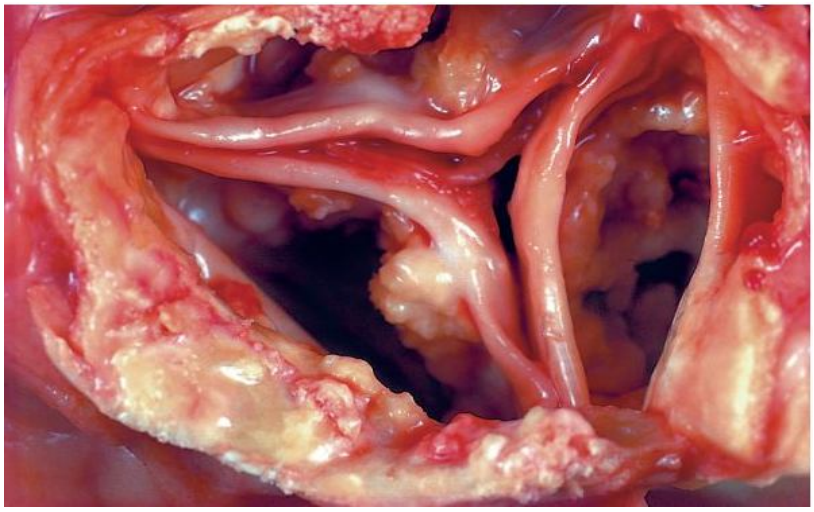


FIGURE 6 *Dystrophic calcification of the aortic valve. View looking down onto the unopened aortic valve in a heart with calcific aortic stenosis. It is markedly narrowed (stenosis). The semilunar cusps are thickened and fibrotic, and behind each cusp are irregular masses of piled-up dystrophic calcification.*

b) **Metastatic Calcification.** Metastatic calcification may occur in normal tissues whenever there is hypercalcemia. Hypercalcemia also accentuates dystrophic calcification.

There are four principal causes of hypercalcemia:

1) Increased secretion of parathyroid hormone (PTH) with subsequent bone resorption, as in *hyperparathyroidism* due to parathyroid tumors, and ectopic secretion of PTH-related protein by malignant tumors.

2) *Destruction of bone tissue*, secondary to primary tumors of bone marrow (e.g., multiple myeloma, leukemia) or diffuse skeletal metastasis (e.g., breast cancer), accelerated bone turnover (e.g., Paget disease), or immobilization
3) *Vitamin D–related disorders*, including vitamin D intoxication, sarcoidosis (in which macrophages activate a vitamin D precursor), and 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.

3.4 Cellular Aging.

Cellular aging is the result of a progressive decline in cellular function and viability caused by genetic abnormalities and the accumulation of cellular and molecular damage due to the effects of exposure to exogenous influences. Studies in model systems have clearly established that aging is a regulated process that is influenced by a limited number of genes, and genetic anomalies underlie syndromes resembling premature aging in humans as well. Such findings suggest that aging is associated with definable mechanistic alterations.

Changes that contribute to cellular aging include the following:

1) *Decreased cellular replication*. The concept that most normal cells have a limited capacity for replication was developed from a simple experimental model for aging. Normal human fibroblasts, when placed in tissue culture, have limited division potential.
2) *Accumulation of metabolic and genetic damage*. Cellular life span is determined by a balance between damage resulting from *metabolic events* occurring within the cell and counteracting molecular responses that can repair the damage. One group of potentially toxic products of normal metabolism are *reactive oxygen species*. As we saw earlier, these by-products of oxidative phosphorylation cause covalent modifications of proteins, lipids, and nucleic acids. Increased oxidative damage could result from repeated environmental exposure to such influences as ionizing radiation, mitochondrial dysfunction, or reduction of antioxidant defense mechanisms with age (e.g., vitamin E, glutathione peroxidase). The amount of oxidative damage, which increases as an organism ages, may be an important cause of senescence.

4.0 CONCLUSION.

Shakespeare probably characterized aging best in his elegant description of the seven ages of man. It begins at the moment of **conception**, involves the **differentiation** and **maturation** of the organism and its cells, at some variable point in time leads to the

progressive loss of functional capacity characteristic of senescence, and ends in **death**. With age there are physiologic **and structural alterations** in almost all organ systems. Aging in individuals is affected to a great extent by genetic factors, diet, social conditions, and occurrence of age-related diseases, such as atherosclerosis, diabetes, and osteoarthritis. In addition, there is good evidence that aging-induced alterations in cells are an important component of the aging of the organism.

5.0 SUMMARY.

This unit teaches us about:

- Clinico-pathological examples of cell injury and necrosis.
- Description of apoptosis and autophagy.
- Types of intracellular accumulations.
- Types of pathologic calcification and
- Cellular aging.

6.0 TUTOR-MARKED ASSIGNMENT.

1) Give two clinic-pathological examples of cell injury and tissue necrosis
2) Differentiate between apoptosis and autophagy.
3) Enumerate the different types of intracellular accumulations that you have learned.
4) What is pathological calcification? Briefly describe the types that you have learned.
5) Write a short note on cellular aging.

7.0 REFERENCES.

- **Robbins and Cotran Pathologic Basis of Diseases. Eight edition.**
- **Essentials of Pathology. By Emanuel Rubin. Third edition.**

UNIT 3: WOUND HEALING.

CONTENTS

1.0 INTRODUCTION.

Wound and wound healing are likely terms that will feature in everyday life of a nurse clinician. A clear understanding of the processes involved is therefore unavoidably paramount.

Injury to cells and tissues sets in motion a series of events that contain the damage and initiate the healing process. This process can be broadly separated into regeneration and repair. Regeneration results in the complete restitution of lost or damaged tissue; repair may restore some original structures but can cause structural derangements. In healthy tissues, healing, in the form of regeneration or repair, occurs after practically any insult that causes tissue destruction, and is essential for the survival of the organism.

2.0 OBJECTIVES: At the end of this unit, you should be able to:

1) Differentiate between tissue regeneration and tissue repair.
2) Explain the mechanisms of tissue and organ regeneration.
3) Describe extracellular matrix and cell-matrix interaction and their importance in wound healing.
4) Organize the processes involved in wound healing.
5) Enumerate the local and systemic factors influencing wound healing.

3.0 MAIN CONTENTS:

3.1 Tissue regeneration and tissue repair.

- ***Regeneration*** *refers to the proliferation of cells and tissues to replace lost structures*, such as the growth of an amputated limb in amphibians. In mammals, whole organs and complex tissues rarely regenerate after injury, and the term is usually applied to processes such as liver growth after partial resection or necrosis, but these processes consist of compensatory growth rather than true regeneration. Tissues with high proliferative capacity, such as the **hematopoietic system and the epithelia of the skin and gastrointestinal (GI) tract, renew themselves continuously and can regenerate after injury, as long as the *stem cells* of these tissues are not destroyed.**
- *Repair most often consists of a combination of regeneration* and *scar formation* by the deposition of collagen. The relative contribution of regeneration and scarring in tissue repair depends on the ability of the tissue to regenerate and the extent of the injury. For instance, a superficial skin wound heals through the regeneration of the surface epithelium. However, scar formation is the predominant healing process that occurs when the extracellular matrix (ECM) framework is damaged by severe injury**.**

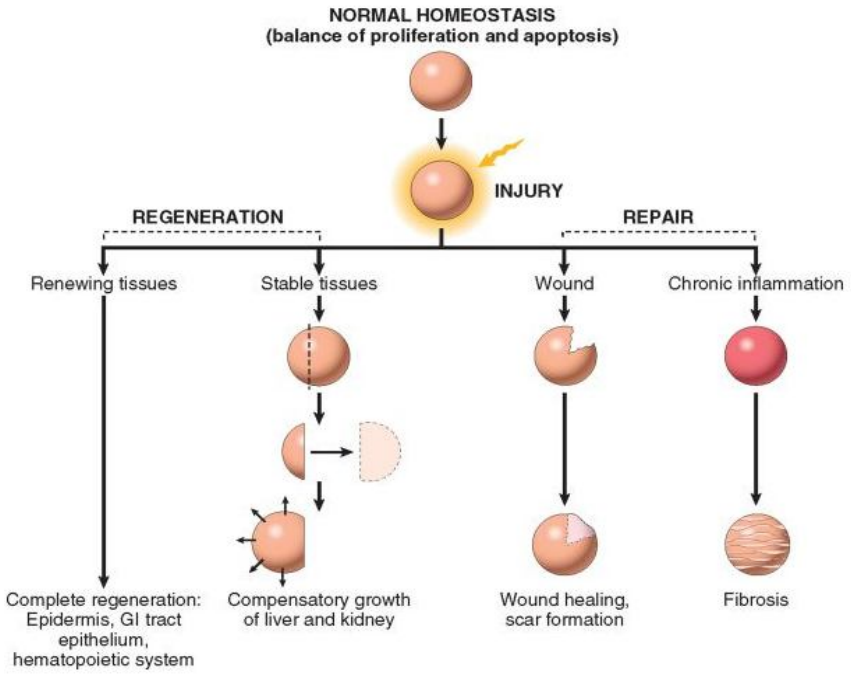


FIGURE 7. Overview of the healing responses after injury. Healing after acute injury can occur by regeneration that restores normal tissue structure or by repair with scar formation. Healing in chronic injury involves scar formation and fibrosis (see text). GI, gastrointestinal.

3.2 Mechanism of Tissue and Organ Regeneration.

As mentioned earlier, urodele amphibians such as the newt can regenerate their tails, limbs, lens, retina, jaws, and even a large portion of the heart, but *the capacity for regeneration of whole tissues and organs has been lost in mammals*.

The inadequacy of true regeneration in mammals has been attributed to the absence of *blastema* formation (the source of cells for regeneration) and to the rapid fibroproliferative response after wounding.

In this section we shall consider the **liver** to illustrate the mechanisms of regeneration, because it has been studied in detail and has important biologic and clinical aspects. Even this process is not one of true regeneration, because the resection of tissue does not cause new growth of liver but instead triggers a process of compensatory hyperplasia in the remaining parts of the organ (discussed below). Other organs, including kidney, pancreas, adrenal glands, thyroid, and the lungs of very young animals, are also capable of compensatory growth, although they display it in less dramatic form than the liver.

Liver regeneration: *The human liver has a remarkable capacity to regenerate, as demonstrated by its growth after partial hepatectomy, which may be performed for tumor resection or for living-donor hepatic transplantation.*

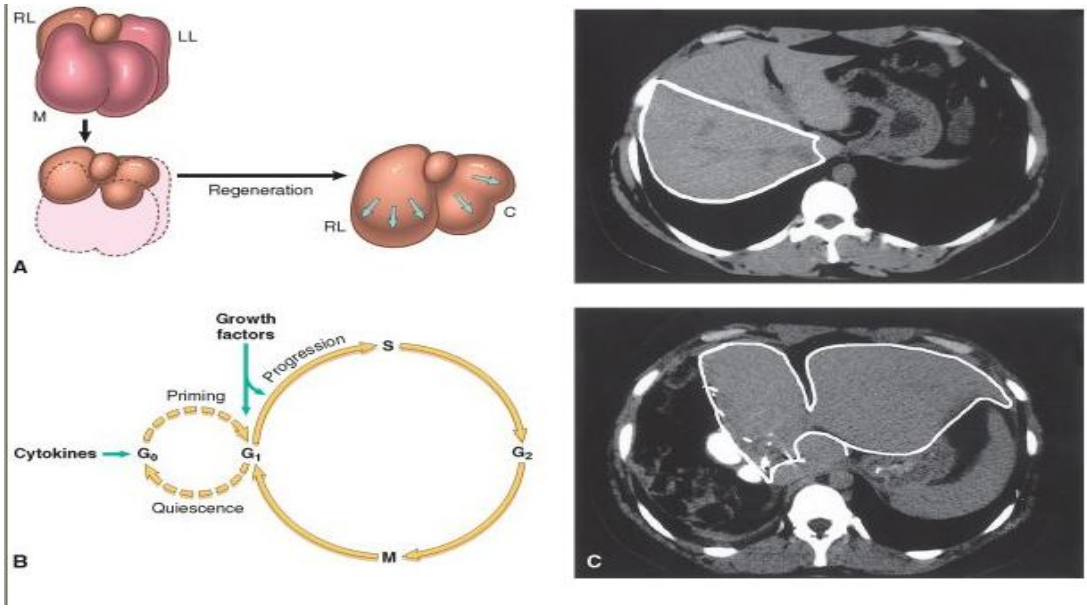


FIGURE 8. Liver regeneration after partial hepatectomy. **A**, The lobes of the liver of a rat (M, median; RL and LL, right and left lateral lobes; C, caudate lobe). Partial hepatectomy removes two thirds of the liver (median and left lateral lobes). After 3 weeks the right lateral and caudate lobes enlarge to reach a mass equivalent to that of the original liver without regrowth of the median and left lateral lobes. **B**, Entry and progression of hepatocytes in the cell cycle (see text for details). **C**, *Regeneration of the human liver in living-donor transplantation*. Computed tomography scans of the donor liver in living-donor hepatic transplantation. Upper panel is a scan of the liver of the donor before the operation. The right lobe, to be used as a transplant, is outlined. Lower panel is a scan of the liver 1 week after performance of partial hepatectomy. Note the great enlargement of the left lobe (outlined in the panel) without regrowth of the right lobe. *(**A**, From Goss RJ: Regeneration versus repair. In Cohen IK et al [eds]: Wound Healing. Biochemical and Clinical Aspects. Philadelphia, WB Saunders, 1992, pp 20–39; **C**, courtesy of R. Troisi, MD, Ghent University, Ghent, Belgium; reproduced in part from Fausto N: Liver regeneration. In Arias I, et al: The Liver: Biology and Pathobiology, 4th ed. Philadelphia, Lippincott Williams & Wilkins, 2001.)*

In humans, resection of approximately 60% of the liver in living donors results in the doubling of the liver remnant in about one month. The portions of the liver that remain after partial hepatectomy constitute an intact “mini-liver” that rapidly expands and reaches the mass of the original liver. Almost all hepatocytes replicate during liver regeneration after partial hepatectomy. Because hepatocytes are quiescent cells, it takes them several hours to enter the cell cycle, progress through G_1, and reach the S phase of DNA replication.

Growth Factors

The proliferation of many cell types is driven by polypeptides known as growth factors. These factors, which can have restricted or multiple cell targets, may also promote cell survival, locomotion, contractility, differentiation, and angiogenesis, activities that may be as important as their growth-promoting effects. All growth factors function as *ligands* that bind to specific *receptors*, which deliver signals to the target cells. These signals stimulate the transcription of genes that may be silent in resting cells, including genes that control *cell cycle entry and progression*. Table 5 lists some of the most important growth factors involved in tissue regeneration and repair. Here we review only those that have major roles in these processes. Other growth factors are alluded to in various sections of the book.

Table 5. Growth Factors and Cytokines Involved in Regeneration and Wound Healing

Growth Factor	Symbol	Source	Functions
Epidermal growth α	EGF	Platelets, macrophages, saliva, urine, milk, plasma	Mitogenic for keratinocytes and fibroblasts; stimulates keratinocyte migration and granulation tissue formation
Transforming growth factor α	TGF-α	Macrophages, T lymphocytes, keratinocytes, and many tissues	Similar to EGF; stimulates replication of hepatocytes and most epithelial cells
Heparin-binding EGF	HB-EGF	Macrophages, mesenchymal cells	Keratinocyte replication
Hepatocyte growth factor/scatter factor	HGF	Mesenchymal cells	Enhances proliferation of hepatocytes, epithelial cells, and endothelial cells; increases cell motility, keratinocyte replication
Vascular endothelial cell growth factor (isoforms A, B, C, D)	VEGF	Many types of cells	Increases vascular permeability; mitogenic for endothelial cells (see Table 3-3); angiogenesis
Platelet-derived growth factor (isoforms A, B, C, D)	PDGF	Platelets, macrophages, endothelial cells, keratinocytes, smooth muscle cells	Chemotactic for PMNs, macrophages, fibroblasts, and smooth muscle cells; activates PMNs, macrophages, and fibroblasts; mitogenic for fibroblasts, endothelial cells, and smooth muscle cells; stimulates production of MMPs, fibronectin, and HA; stimulates angiogenesis and wound contraction
Fibroblast growth factor 1 (acidic), 2 (basic), and family	FGF	Macrophages, mast cells, T lymphocytes, endothelial cells,	Chemotactic for fibroblasts; mitogenic for fibroblasts and keratinocytes; stimulates keratinocyte migration,

Growth Factor	Symbol	Source	Functions
		fibroblasts	angiogenesis, wound contraction, and matrix deposition
Transforming growth factor β (isoforms 1, 2, 3); other members of the family are BMPs and activin	TGF-β	Platelets, T lymphocytes, macrophages, endothelial cells, keratinocytes, smooth muscle cells, fibroblasts	Chemotactic for PMNs, macrophages, lymphocytes, fibroblasts, and smooth muscle cells; stimulates TIMP synthesis, angiogenesis, and fibroplasia; inhibits production of MMPs and keratinocyte proliferation
Keratinocyte growth factor (also called FGF-7)	KGF	Fibroblasts	Stimulates keratinocyte migration, proliferation, and differentiation
Tumor necrosis factor	TNF	Macrophages, mast cells, T lymphocytes	Activates macrophages; regulates other cytokines; multiple functions

Modified from Schwartz SI: Principles of Surgery. New York, McGraw-Hill, 1999.

BMP, bone morphogenetic proteins; HA, hyaluronate; MMPs, matrix metalloproteinases; PMNs, polymorphonuclear leukocytes; TIMP, tissue inhibitor of MMP.

3.3 Extracellular Matrix and Cell-Matrix Interactions

Tissue repair and regeneration depend not only on the activity of soluble factors, but also on interactions between cells and the components of the *extracellular matrix (ECM)*. The ECM regulates the growth, proliferation, movement, and differentiation of the cells living within it. It is constantly remodeling, and its synthesis and degradation accompanies morphogenesis, regeneration, wound healing, chronic fibrotic processes, tumor invasion, and metastasis. The ECM sequesters water, providing turgor to soft tissues, and minerals that give rigidity to bone, but it does much more than just fill the spaces around cells to maintain tissue structure. Its various functions include:

- *Mechanical support* for cell anchorage and cell migration, and maintenance of cell polarity
- *Control of cell growth*. ECM components can regulate cell proliferation by signaling through cellular receptors of the integrin family.
- *Maintenance of cell differentiation*. The type of ECM proteins can affect the degree of differentiation of the cells in the tissue, also acting largely via cell surface integrin.
- *Scaffolding for tissue renewal*. The maintenance of normal tissue structure requires a basement membrane or stroma scaffold. The integrity of the basement membrane or the stroma of the parenchymal cells is critical for the organized regeneration of tissues. It is particularly noteworthy that although labile and stable cells are capable of regeneration, injury to these

tissues results in restitution of the normal structure only if the ECM is not damaged. Disruption of these structures leads to collagen deposition and scar formation.

- *Establishment of tissue microenvironments*. Basement membrane acts as a boundary between epithelium and underlying connective tissue and also forms part of the filtration apparatus in the kidney.
- *Storage and presentation of regulatory molecules*. For example, growth factors like FGF and HGF are secreted and stored in the ECM in some tissues. This allows the rapid deployment of growth factors after local injury, or during regeneration.

The ECM is composed of three groups of macromolecules:

- *Fibrous structural proteins*, such as collagens and elastins that provide tensile strength and recoil;
- *Adhesive glycoproteins* that connect the matrix elements to one another and to cells and;
- *Proteoglycans and hyaluronan* that provide resilience and lubrication.

These molecules assemble to form **two basic forms of ECM:**

1) *Interstitial matrix and*
2) *Basement membranes*.

The ***interstitial matrix*** is found in spaces between epithelial, endothelial, and smooth muscle cells, as well as in connective tissue. It consists mostly of fibrillar and nonfibrillar collagen, elastin, fibronectin, proteoglycans, and hyaluronan.

The ***basement membranes*** are closely associated with cell surfaces, and consist of nonfibrillar collagen (mostly type IV), laminin, heparin sulfate, and proteoglycans.

Cell Adhesion Proteins:

*Most adhesion proteins, also called **CAMS** (cell adhesion molecules),form cross-linkages between cells and the ground matrix. They can be classified into four main families: **immunoglobulin family cams**, **cadherins**, **integrins**, and **selectins***. These proteins function as trans-membrane receptors but are sometimes stored in the cytoplasm.

3.4 Healing by Repair and Scar Formation.

If tissue injury is severe or chronic, and results in damage of both parenchymal cells and the stromal framework of the tissue, healing cannot be accomplished by regeneration. Under these conditions, the main healing process is *repair by deposition of collagen and other ECM components, causing the formation of* a *scar*. In contrast to regeneration which involves the restitution of tissue components, repair is a fibroproliferative response that "patches" rather than restores the tissue. 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.

Repair by connective tissue deposition includes the following basic features: ***inflammation, angiogenesis, migration and proliferation of fibroblast, scar formation and connective tissue remodeling.***

3.4.1 Cutaneous Wound Healing.

As a prototype repair process, cutaneous wound healing shall be considered.

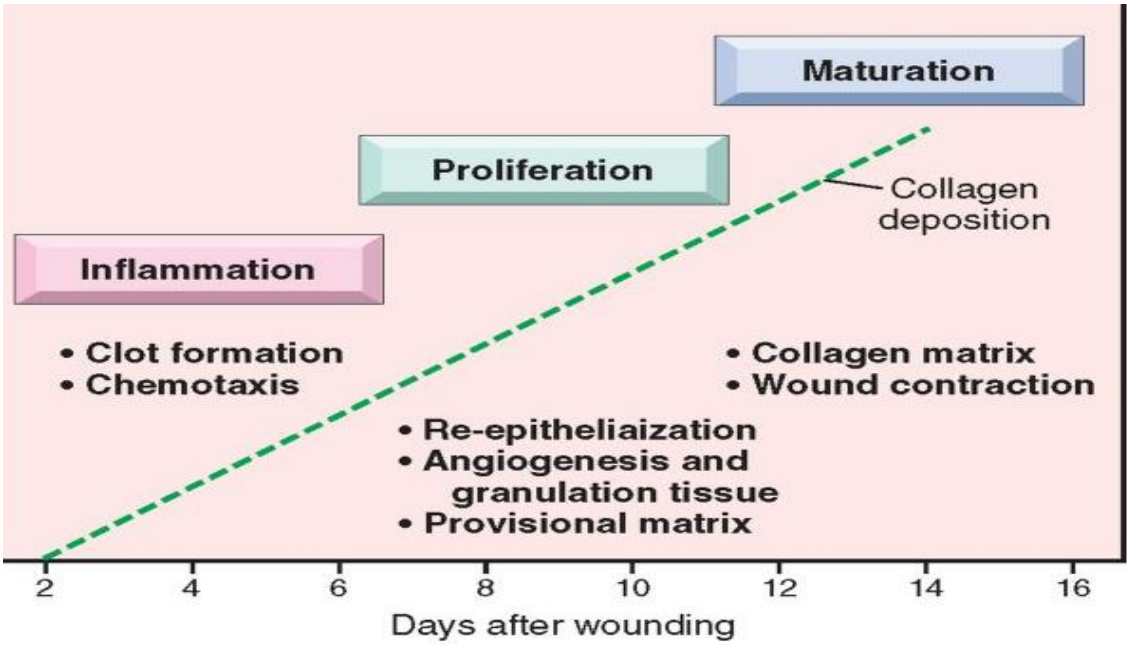


FIGURE 9 Phases of cutaneous wound healing: inflammation, proliferation, and maturation (see text for details). *(Modified from Broughton G et al: The basic science of wound healing. Plast Reconstr Surg 117:12S–34S, 2006.)*

Cutaneous wound healing is divided into three phases: inflammation, proliferation, and maturation (Fig. 9). These phases overlap, and their separation is somewhat arbitrary, but they help to understand the sequence of events that take place in the healing of skin wounds. The initial injury causes platelet adhesion and aggregation and the formation of a clot in the surface of the wound, leading to *inflammation*. In the *proliferative phase* there is formation of granulation tissue, proliferation and migration of connective tissue cells, and re-epithelialization of the wound surface. *Maturation* involves ECM deposition, tissue remodeling, and wound contraction.

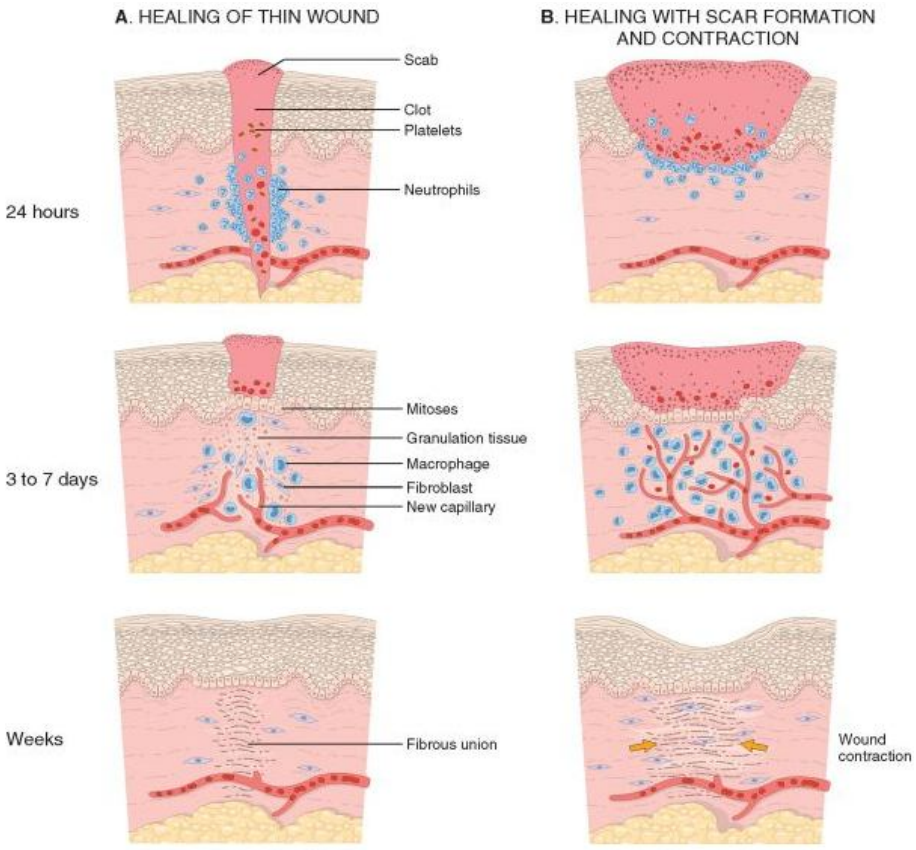


FIGURE 10 Wound healing and scar formation. A, Healing of wound that caused little loss of tissue: note the small amount of granulation tissue, and formation of a thin scar with minimal contraction. B, Healing of large wound: note large amounts of granulation tissue and scar tissue, and wound contraction.

The simplest type of cutaneous wound repair is the healing of a clean, uninfected surgical incision approximated by surgical sutures (Fig. 10A above). Such healing is referred to as *healing by primary union* or *by first intention.*

The incision causes death of a limited number of epithelial and connective tissue cells and disruption of epithelial basement membrane continuity. *Re-epithelialization to close the wound occurs with formation of a relatively thin scar*.

The repair process is more complicated in excisional wounds (figure 10B above) that create large defects on the skin surface, causing extensive loss of cells and tissue. *The healing of these wounds involves a more intense inflammatory reaction, the formation of abundant granulation tissue (described below), and extensive collagen deposition, leading to the formation of a substantial scar, which generally contracts*. This form of healing is referred to as *healing by secondary union* or *by second intention (fig 11).*

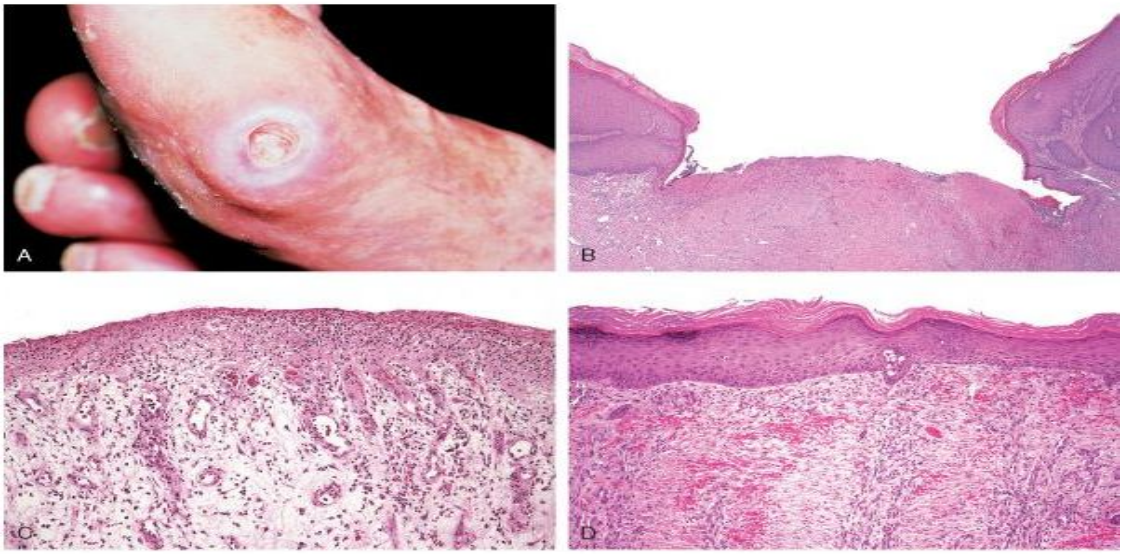


FIGURE 11. Healing of skin ulcers. A, Pressure ulcer of the skin, commonly found in diabetic patients. The histologic slides show: B, a skin ulcer with a large gap between the edges of the lesion; C, a thin layer of epidermal re-epithelialization and extensive granulation tissue formation in the dermis; and D, continuing re-epithelialization of the epidermis and wound contraction. *(Courtesy of Z. Argenyi, MD, University of Washington, Seattle, WA.)*

3.4.2 Growth Factors and Cytokines Affecting Various Steps in Wound Healing.

A large number of growth factors and cytokines are involved in cutaneous wound healing. The main agents, and the steps at which they participate in the repair process, are listed in Table 6.

TABLE 6. Growth Factors and Cytokines Affecting Various Steps in Wound Healing

Monocyte chemotaxis	Chemokines, TNF, PDGF, FGF, TGF-β
Fibroblast migration/replication	PDGF, EGF, FGF, TGF-β, TNF, IL-1
Keratinocyte replication	HB-EGF, FGF-7, HGF
Angiogenesis	VEGF, angiopoietins, FGF
Collagen synthesis	TGF-β, PDGF
Collagenase secretion	PDGF, FGF, TNF; TGF-β inhibits

HB-EGF, heparin-binding EGF; IL-1, interleukin 1; TNF, tumor necrosis factor; other abbreviations as given in Table 5.

3.4.3 Steps Involved in Wound Healing.

Formation of Blood Clot.

Wounding causes the rapid activation of coagulation pathways, which results in *the formation of a blood clot on the wound surface*. In addition to entrapped red cells, the clot contains fibrin, fibronectin, and complement components. *The clot serves to stop bleeding and also as a scaffold for migrating cells, which are attracted by growth factors, cytokines and chemokines released into the area.*

Formation of Granulation Tissue.

Fibroblasts and vascular endothelial cells proliferate in the first 24 to 72 hours of the repair process to form a specialized type of tissue called *granulation tissue*, which is a hallmark of tissue repair. The term derives from its pink, soft, granular appearance on the surface of wounds. Its characteristic histologic feature is *the presence of new small blood vessels (angiogenesis) and the proliferation of fibroblasts*. These new vessels are leaky, allowing the passage of plasma proteins and fluid into the extravascular space. Thus, new granulation tissue is often edematous. Granulation tissue progressively invades the incision space; 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*. Hence, it is much more prominent in healing by secondary union. By 5 to 7 days, granulation tissue fills the wound area and neovascularization is maximal.

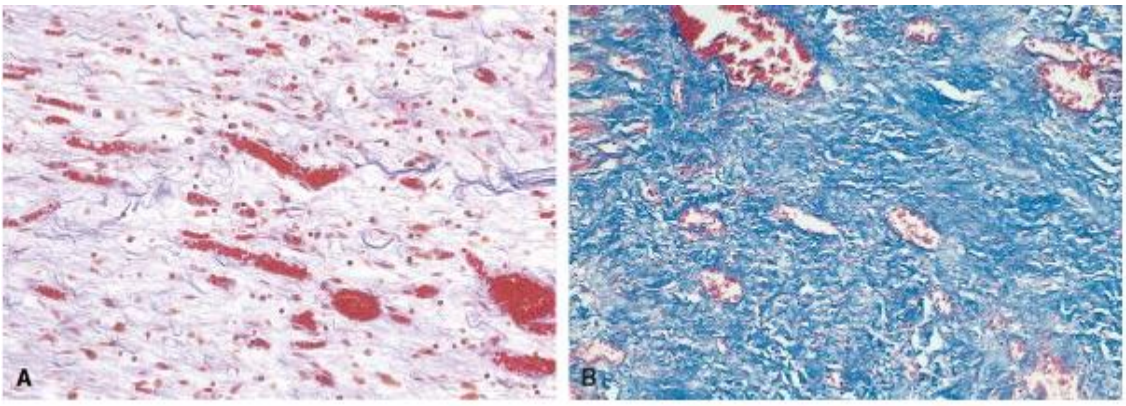


FIGURE 12. A, Granulation tissue showing numerous blood vessels, edema, and loose ECM containing occasional inflammatory cells. Collagen is stained blue by the trichrome stain; minimal mature collagen can be seen at this point. B, Trichrome stain of mature scar, showing dense collagen, with only scattered vascular channels.

Cell Proliferation and Collagen Deposition.

Neutrophils are largely replaced by *macrophages* by 48 to 96 hours. *Macrophages are key cellular constituents of tissue repair*, clearing extracellular debris, fibrin, and other foreign material at the site of repair, and promoting angiogenesis and ECM deposition.

Scar Formation.

The leukocytic infiltrate, edema, and increased vascularity largely disappear during the second week. Blanching begins, accomplished by the increased accumulation of collagen within the wound area and regression of vascular channels. Ultimately, the original granulation tissue scaffolding is converted into a pale, avascular scar, composed of spindle-shaped fibroblasts, dense collagen, fragments of elastic tissue, and other ECM components.

Wound Contraction.

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.

Connective Tissue Remodeling.

The replacement of granulation tissue with a scar involves changes in the composition of the ECM. The balance between ECM synthesis and degradation results in remodeling of the connective tissue framework – an important feature of tissue repair. Some of the growth factors that stimulate synthesis of collagen and other connective tissue molecules also modulate the synthesis and activation of metalloproteinases, enzymes that degrade these ECM components.

Degradation of collagen and other ECM proteins is achieved by matrix metalloproteinases (MMPs), a family of enzymes that includes more than 20 members that have in common a 180-residue zinc-protease domain (MMPs should be distinguished from neutrophils elastase, cathepsin G, kinins, plasmin, and other important proteolytic enzymes, which also degrade EMC components and which are *serine proteinases, not metalloenzymes*).

Recovery of Tensile Strength.

Fibrillar collagens (mostly type I collagen) form a major portion of the connective tissue in repair sites and are essential for the development of strength in healing wounds. *Net collagen accumulation, however, depends not only on increased collagen synthesis but also on decreased degradation.*

3.4.4. Local and Systemic Factors that Influence Wound Healing.

The adequacy of wound repair may be impaired by systemic and local host factors.

Systemic factors include those listed below:

- *Nutrition* has profound effects on wound healing. Protein deficiency, for example, and particularly vitamin C deficiency, inhibit collagen synthesis and retard healing.
- *Metabolic status* can change wound healing. Diabetes mellitus, for example, is associated with delayed healing, as a consequence of the microangiopathy that is a frequent feature of this disease.
- *Circulatory status* can modulate wound healing. *Inadequate blood supply*, usually caused by arteriosclerosis or venous abnormalities (e.g., varicose veins) that retard venous drainage, also impairs healing.
- *Hormones* such as *glucocorticoids* have well-documented anti-inflammatory effects that influence various components of inflammation. These agents also inhibit collagen synthesis.

Local factors that influence healing include:

- *Infection* is the single most important cause of delay in healing, because it results in persistent tissue injury and inflammation.
- *Mechanical factors*, such as early motion of wounds, can delay healing, by compressing blood vessels and separating the edges of the wound.
- *Foreign bodies*, such as unnecessary sutures or fragments of steel, glass, or even bone, constitute impediments to healing.
- *Size, location, and type of wound*. Wounds in richly vascularized areas, such as the face, heal faster than those in poorly vascularized ones, such as the foot. As we have discussed, small incisional injuries heal faster and with less scar formation than large excisional wounds or wounds caused by blunt trauma.

3.4.5 Pathologic Aspects of Repair

Complications in wound healing can arise from abnormalities in any of the basic components of the repair process. These aberrations can be grouped into three general categories:

(1) Deficient scar formation.

Inadequate formation of granulation tissue or assembly of a scar can lead to two types of complications: wound dehiscence and ulceration.

(2) Excessive formation of the repair components.

Excessive formation of the components of the repair process can give rise to hypertrophic scars and keloids (see figure 13).

FIGURE 13. Keloid. A, Excess collagen deposition in the skin forming a raised scar known as keloid. B, Note the thick connective tissue deposition in the dermis. *(A, from Murphy GF, Herzberg AJ: Atlas of Dermatopathology. Philadelphia, WB Saunders, 1996, p 219; B, courtesy of Z. Argenyi, MD, University of Washington, Seattle, WA.)*

(3) 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

FIGURE 14.Wound contracture. Severe contracture of a wound after deep burn injury. *(From Aarabi S et al: Hypertrophic scar formation following burns and trauma: new approaches to treatment. PLOS Med 4:e234, 2007.)*

4.0 CONCLUSION.

Since exposures to noxious environmental hazards are inevitable, the human species therefore, must develop mechanisms to regenerate or repair tissue damage. The knowledge of the sequence of events involved in the healing processes will be brought to bear on everyday encounter of the nurse clinician.

5.0 SUMMARY: This unit teaches us about:

- The differences between tissue regeneration and repair.
- The mechanisms of tissue and organ regeneration.
- Extracellular matrix and cell-matrix interaction and their importance in wound healing.
- The processes involved in wound healing.
- The local and systemic factors influencing wound healing.
- Pathologic aspect of wound healing.

6.0 TUTOR-MARKED ASSIGNMENT.

- Differentiate between tissue regeneration and repair.
- Describe briefly the mechanisms involved in tissue and organ regeneration.
- What are the roles of extracellular matrix in wound healing? Mention the groups that you know.
- What are cell adhesion molecules? Give examples.
- Briefly describe the processes and steps involved in wound healing.
- List local and systemic factors influencing wound healing.
- List the pathological aspects of wound healing, that you have learned. Give examples.

7.0 REFERENCES.

- **Robbins and Cotran Pathologic Basis of Diseases. Eight edition.**
- **Essentials of Pathology. By Emanuel Rubin. Third edition.**

MODULE 3

UNIT 1: PATHOLOGY AND PATHOGENESIS OF OEDEMA

CONTENTS

1.0 INTRODUCTION

Approximately 60% of lean body weight is water. Two thirds of the body's water is intracellular, and the remainder is in extracellular compartments, mostly the interstitium (or third space) that lies between cells; only about 5% of total body water is in blood plasma.

The movement of water and low molecular weight solutes such as salts between the intravascular and interstitial spaces is controlled primarily by the opposing effect of vascular hydrostatic pressure and plasma colloid osmotic pressure. Normally the outflow of fluid from the arteriolar end of the microcirculation into the interstitium is nearly balanced by inflow at the venular end; a small residual amount of fluid may be left in the interstitium and is drained by the lymphatic vessels, ultimately returning to the bloodstream via the thoracic duct.

Either increased capillary pressure or diminished colloid osmotic pressure can result in increased interstitial fluid (Figure 15). If the movement of water into tissues (or body cavities) exceeds lymphatic drainage, fluid accumulates. An abnormal increase in interstitial fluid within tissues is called *OEDEMA*, while fluid collections in the different body cavities are variously designated *hydrothorax, hydropericardium, and hydroperitoneum* (the last is more commonly called *ascites*). *Anasarca* is a severe and generalized edema with widespread subcutaneous tissue swelling.

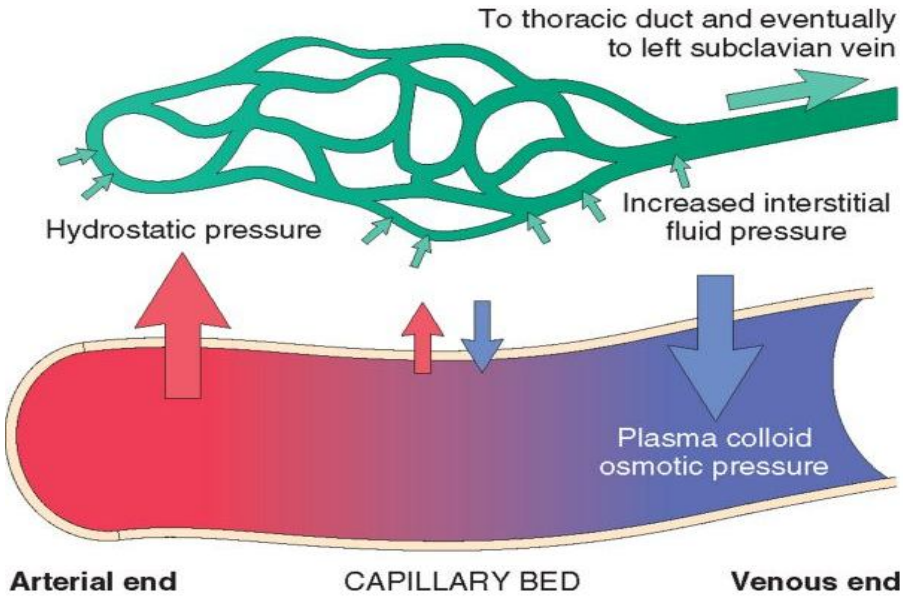


FIGURE 15. Factors influencing fluid transit across capillary walls. Capillary hydrostatic and osmotic forces are normally balanced so that there is no *net* loss or gain of fluid across the capillary bed. However, *increased* hydrostatic pressure or *diminished* plasma osmotic pressure will cause extravascular fluid to accumulate. Tissue lymphatics remove much of the excess volume, eventually returning it to the circulation via the thoracic duct; however, if the capacity for lymphatic drainage is exceeded, tissue *edema* results.

2.0 OBJECTIVES:

At the end of this unit, you should be able to:

1) List and describe the pathophysiologic categories of oedema.

2) List examples of clinical conditions that give rise to each category.

3.0 MAIN CONTENTS.

3.1 PATHOPHYSIOLOGIC CATEGORIES OF OEDEMA.

Oedema caused by increased hydrostatic pressure or reduced plasma protein is typically a protein-poor fluid called a *transudate*. Oedema fluid of this type is seen in patients suffering from heart failure, renal failure, hepatic failure, and certain forms of malnutrition, as described below and outlined in Figure 16. In contrast, inflammatory oedema is a protein-rich *exudate* that is a result of increased vascular permeability.

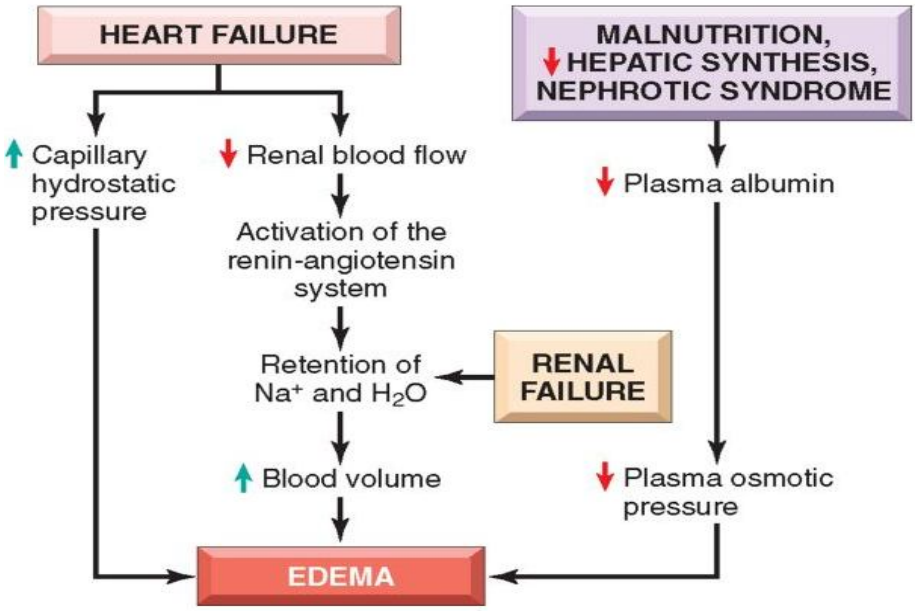


FIGURE 16. Pathways leading to systemic edema from primary heart failure, primary renal failure, or reduced plasma osmotic pressure (e.g., from malnutrition, diminished hepatic synthesis, or protein loss from nephrotic syndrome).

TABLE 7. Pathophysiologic Categories of Oedema

INCREASED HYDROSTATIC PRESSURE
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 Arteriolar dilation Heat Neurohumoral dysregulation
REDUCED PLASMA OSMOTIC PRESSURE (HYPOPROTEINEMIA)
Protein-losing glomerulopathies (nephrotic syndrome) Liver cirrhosis (ascites) Malnutrition Protein-losing gastroenteropathy
LYMPHATIC OBSTRUCTION
Inflammatory Neoplastic Postsurgical Postirradiation
SODIUM RETENTION
Excessive salt intake with renal insufficiency Increased tubular reabsorption of sodium Renal hypoperfusion

Increased renin-angiotensin-aldosterone secretion
INFLAMMATION
Acute inflammation Chronic inflammation Angiogenesis

Modified from Leaf A, Cotran RS: Renal Pathophysiology, 3rd ed. New York, Oxford University Press, 1985, p 146.

3.1.1 Increased Hydrostatic Pressure.

Regional increases in hydrostatic pressure can result from a focal impairment in venous return. Thus, *deep venous thrombosis* in a lower extremity may cause localized oedema in the affected leg. On the other hand, *generalized increases* in venous pressure, with resulting systemic oedema, occur most commonly in *congestive heart failure,* where compromised right ventricular function leads to pooling of blood on the venous side of the circulation.

3.1.2 Reduced Plasma Osmotic Pressure.

This **occurs** when albumin, the major plasma protein, is not synthesized in adequate amounts or is lost from the circulation. An important cause of albumin loss is the *nephrotic syndrome* in which glomerular capillaries become leaky; patients typically present with generalized oedema. Reduced albumin synthesis occurs in the setting of severe liver diseases (e.g., cirrhosis) or in protein malnutrition.

3.1.3 Sodium and Water Retention.

Increased salt retention—with obligate associated water—causes both increased hydrostatic pressure (due to intravascular fluid volume expansion) and diminished vascular colloid osmotic pressure (due to dilution).

3.1.4 Lymphatic Obstruction.

Impaired lymphatic drainage results in *lymphoedema* that is typically localized; causes include chronic inflammation with fibrosis, invasive malignant tumors, physical disruption, radiation damage, and certain infectious agents. One dramatic example is seen in parasitic *filariasis*, in which lymphatic obstruction due to extensive inguinal lymphatic and lymph node fibrosis can result in oedema of the external genitalia and lower limbs that is so massive as to earn the appellation *elephantiasis*. Severe oedema of the upper extremity may also complicate surgical removal and/or irradiation of the breast and associated axillary lymph nodes in patients with breast cancer.

3.1.5 Inflammation. (See table 7 above).

4.0 CONCLUSION.

The consequences of oedema range from merely annoying to rapidly fatal. Subcutaneous tissue oedema is important primarily because it signals potential underlying cardiac or renal disease; however, when significant, it can also impair wound healing or the clearance of infection. Pulmonary oedema is a common clinical problem that is most frequently seen in the setting of left ventricular failure; it can also occur with renal failure, acute respiratory

distress syndrome, pulmonary inflammation or infection. Not only does fluid collect in the alveolar septa around capillaries and impede oxygen diffusion, but oedema fluid in the alveolar spaces also creates a favourable environment for bacterial infection. Brain oedema is life-threatening; if severe, brain substance can *herniate* (extrude) through the foramen magnum, or the brain stem vascular supply can be compressed. Either condition can injure the medullary centers and cause death.

5.0 SUMMARY. This unit teaches us about:

- The pathophysiological mechanisms involved in the formation of the various categories of oedema.
- The clinicopathological examples in each category.

6.0 TUTOR-MARKED ASSIGNMENTS.

- List and explain briefly the pathophysiological mechanisms involved in the formation of oedema. Give examples of clinical settings in which each category occurs.

7.0 REFERENCES AND FURTHER READING.

- **Robbins and Cotran Pathologic Basis of Diseases. Eight edition.**
- **Essentials of Pathology. By Emanuel Rubin. Third edition.**

UNIT 2: SHOCK: PATHOLOGY AND PATHOGENESIS

CONTENTS

1.0 INTRODUCTION:

The modality and effectiveness of any form of resuscitative protocol employed in the daily nursing practice will depend largely on a sound understanding of the cascade of events involved in shock.

Shock is the final common pathway for several potentially lethal clinical events, including severe hemorrhage, extensive trauma or burns, large myocardial infarction, massive pulmonary embolism, and microbial sepsis.

2.0 OBJECTIVES:

At the end of this unit, you should be able to:

1) Define shock.
2) List and describe the 3 common categories of shock.
3) Talk about other less common types of shock.
4) Itemize the processes involved in the pathogenesis of septic shock.
5) Describe the stages of shock.
6) Mention the clinical consequences of shock.

3.0 MAIN CONTENTS.

3.1 Definition of Shock.

Shock is characterized by systemic hypotension due either to reduced cardiac output or to reduced effective circulating blood volume. The consequences are *impaired tissue perfusion and cellular hypoxia*. At the outset the cellular injury is reversible; however, prolonged shock eventually leads to irreversible tissue injury that often proves fatal.

3.2 The Three General Categories of Shock.

The causes of shock fall into three general categories (see Table 8):

- *1) Cardiogenic shock* results from low cardiac output due to myocardial pump failure. This can be due to intrinsic myocardial damage (infarction), ventricular arrhythmias, extrinsic compression (e.g cardiac tamponade), or outflow obstruction (e.g., pulmonary embolism).
- *Hypovolemic shock* results from low cardiac output due to the loss of blood or plasma volume, such as can occur with massive hemorrhage or fluid loss from severe burns.
- *Septic shock* results from vasodilation and peripheral pooling of blood as part of a systemic immune reaction to bacterial or fungal infection. Its complex pathogenesis will be discussed in further details.

TABLE 8. Three Major categories of Shock

Type of Shock	Clinical Example	Principal Mechanisms
CARDIOGENIC		
	Myocardial infarction Ventricular rupture Arrhythmia Cardiac tamponade Pulmonary embolism	Failure of myocardial pump resulting from intrinsic myocardial damage, extrinsic pressure, or obstruction to outflow
HYPOVOLEMIC		
	Fluid loss (e.g., hemorrhage, vomiting, diarrhea, burns, or trauma)	Inadequate blood or plasma volume
SEPTIC		
	Overwhelming microbial infections (bacterial and fungal) Superantigens (e.g., toxic shock syndrome)	Peripheral vasodilation and pooling of blood; endothelial activation/injury; leukocyte-induced damage, disseminated intravascular coagulation; activation of cytokine cascades

3.3 Other less common types of shock.

Less commonly, shock can occur in the setting of anesthetic accident or a spinal cord injury *(neurogenic shock)*, as a result of loss of vascular tone and peripheral pooling of blood. *Anaphylactic shock* denotes systemic vasodilation and increased vascular permeability caused by an IgE–mediated hypersensitivity reaction.

In these situations, acute widespread vasodilation results in tissue hypoperfusion and hypoxia.

3.4 Pathogenesis of Septic Shock.

Septic shock is associated with severe haemodynamic and haemostatic derangements, and therefore merits more detailed consideration here.

With a mortality rate near 20%, septic shock ranks first among the causes of death in intensive care units and accounts for over 200,000 lost lives each year in the United States. Its incidence is rising, ironically due to improvements in life support for critically ill patients and the growing ranks of immunocompromised hosts (due to chemotherapy, immunosuppressant, or HIV infection). 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.

In septic shock, systemic vasodilation and pooling of blood in the periphery leads to tissue hypoperfusion, even though cardiac output may be preserved or even increased early in the course. This is accompanied by widespread endothelial cell activation and injury, often leading to a hypercoagulable state that can manifest as DIC. In addition, septic shock is associated with changes in metabolism that directly suppress cellular function. The net effect of these abnormalities is hypoperfusion and dysfunction of multiple organs—culminating in the extraordinary morbidity and mortality associated with sepsis.

The major factors contributing to the pathophysiologic of septic shock include the followings:

1) *Inflammatory mediators*. Various microbial cell wall constituents engage receptors on neutrophils, mononuclear inflammatory cells, and endothelial cells, leading to cellular activation.
2) *Endothelial cell activation and injury*. Endothelial cell activation by microbial constituents or inflammatory mediators produced by leukocytes has three major sequelae: (1) thrombosis; (2) increased vascular permeability; and (3) vasodilation. *The derangement in coagulation is sufficient to produce the fearsome complication of DIC in up to half of septic patients.*
3) *Metabolic abnormalities*. Septic patients exhibit insulin resistance and hyperglycemia. Cytokines such as TNF and IL-1, stress-induced hormones (such as glucagon, growth hormone, and glucocorticoids), and catecholamines all drive gluconeogenesis. At the same time, the pro-inflammatory cytokines suppress insulin release while simultaneously promoting insulin resistance in the liver and other tissues, likely by impairing the surface expression of GLUT-4, a glucose transporter. *Hyperglycemia decreases neutrophil function—thereby suppressing bactericidal activity—and causes increased adhesion molecule expression on endothelial cells*. Although sepsis is initially associated with an acute surge in glucocorticoids production, this phase is frequently followed by adrenal insufficiency and a functional deficit of glucocorticoids. This may stem from depression of the synthetic capacity of intact adrenal glands or frank adrenal necrosis due to DIC (*Waterhouse-Friderichsen syndrome).*
4) *Immune suppression*. The hyperinflammatory state initiated by sepsis can activate counter-regulatory immunosuppressive mechanisms, which may involve both innate and adaptive immunity.
5) *Organ dysfunction*. Systemic hypotension, interstitial edema, and small vessel thrombosis all decrease the delivery of oxygen and nutrients to the tissues, which fail to properly utilize those nutrients that are delivered due to changes in cellular metabolism. High levels of cytokines and secondary mediators may diminish myocardial contractility and cardiac output, and increased vascular permeability and endothelial injury can lead to the *adult respiratory distress syndrome*. Ultimately, these factors may conspire to cause the failure of multiple organs, particularly the kidneys, liver, lungs, and heart, culminating in death.

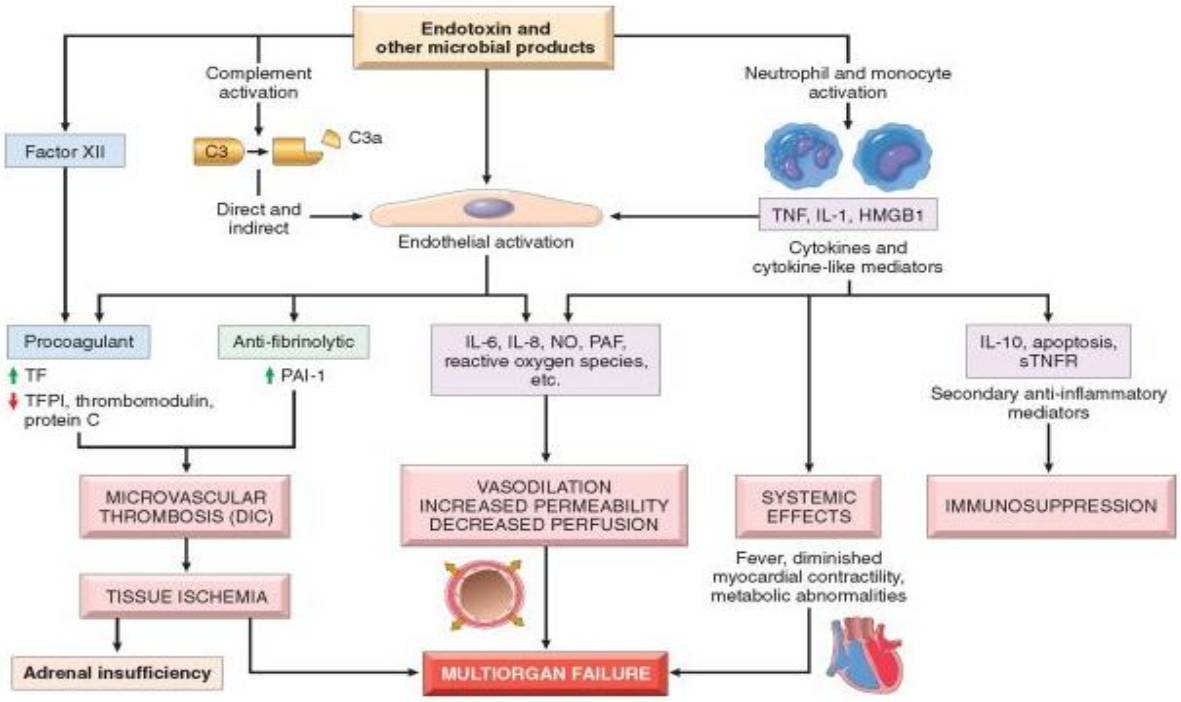


FIGURE 17. Major pathogenic pathways in septic shock. Microbial products activate endothelial cells and cellular and humoral elements of the innate immune system, initiating a cascade of events that lead to end-stage multiorgan failure. Additional details are given in the text. DIC, disseminated vascular coagulation; HMGB1, high mobility group box 1 protein; NO, nitric oxide; PAF, platelet activating factor; PAI-1, plasminogen activator inhibitor 1; STNFR, soluble TNF receptor; TF, tissue factor; TFPI, tissue factor pathway inhibitor.

The severity and outcome of septic shock are likely dependent upon the following:

1) Extent and virulence of the infection;
2) The immune status of the host;
3) The presence of other co-morbid conditions;
4) The pattern and level of mediator production.

The multiplicity of factors and the complexity of the interactions that underlie sepsis explain why most attempts to intervene therapeutically with antagonists of specific mediators have been of very modest benefit at best, and may even have had deleterious effects in some cases.

The standard of care remains:

- Treatment with appropriate (broad-spectrum)antibiotics,
- Intensive insulin therapy for hyperglycemia,
- Fluid resuscitation to maintain systemic pressures,

- Physiologic dose of corticosteroids to correct relative adrenal insufficiency.
- Administration of activated protein C (to prevent thrombin generation and thereby reduce coagulation and inflammation) may have some benefit in cases of severe sepsis, but this remains controversial.

Suffice it to say, even in the best of clinical centers, septic shock remains an obstinate clinical challenge.

3.5 The Stages of Shock.

Shock is a progressive disorder that, if uncorrected, leads to death. The exact mechanism(s) of death from sepsis are still unclear; aside from increased lymphocyte and enterocyte apoptosis there is only minimal cell death, and patients rarely have refractory hypotension. For hypovolemic and cardiogenic shock, however, the pathways to death are reasonably well understood. Unless the insult is massive and rapidly lethal (e.g., a massive hemorrhage from a ruptured aortic aneurysm), shock in those settings tends to evolve through three general (albeit somewhat artificial) phases:

- 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.

3.6 Clinical Consequences.

The clinical manifestations of shock depend on the precipitating insult.

In hypovolemic and cardiogenic shock *the patient presents with hypotension; a weak, rapid pulse; tachypnea; and cool, clammy, cyanotic skin*. In septic shock *the skin may initially be warm and flushed because of peripheral vasodilation*. The initial threat to life stems from the underlying catastrophe that precipitated the shock (e.g., myocardial infarct, severe hemorrhage, or sepsis). Rapidly, however, the cardiac, cerebral, and pulmonary changes secondary to shock worsen the problem. Eventually, electrolyte disturbances and metabolic acidosis also exacerbate the situation. Individuals who survive the initial complications may enter *a second phase dominated by renal insufficiency* and marked by a progressive fall in urine output as well as severe fluid and electrolyte imbalances.

4.0 CONCLUSION.

Shock is a progressive disorder that, if uncorrected, leads to death; hence appropriate measure(s) should be meted out, and that early.

The prognosis varies with the origin of shock and its duration. Thus, greater than 90% of young, otherwise healthy patients with hypovolemic shock survive with appropriate management; in

comparison, septic shock, or cardiogenic shock associated with extensive myocardial infarction, can have substantially worse mortality rates, even with optimal care.

5.0 SUMMARY. This unit teaches us about:

1) The various categories of shock and clinical settings precipitating them.

2) The pathogenesis of septic shock, the frequently encountered type, whose course is still poorly understood.

3) the stages of shock.

6.0 TUTOR-MARKED ASSIGNMENT.

1. What is shock? Enumerate and briefly talk about the various categories of shock.
2. Describe septic shock. What are the processes involved?
3. Describe briefly the stages of shock that you have learned.

7.0 REFERENCES AND FURTHER READING.

- **Robbins and Cotran Pathologic Basis of Diseases. Eight edition**

MODULE 4

UNIT 1: ABNORMALITIES OF CELL GROWTH AND DIFFERENTIATION.

CONTENTS

1.0 INTRODUCTION.

In adult tissue, the size of cell populations is determined by the rates of cell proliferation, differentiation, and death by apoptosis (Figure 18), and increased cell numbers may result from either increased proliferation or decreased cell death. *Apoptosis,* as earlier considered, is a physiologic process required for tissue homeostasis, but it can also be induced by a variety of pathologic stimuli. Differentiated cells incapable of replication are referred to as *terminally differentiated* cells. The impact of *differentiation* depends on the tissue under which it occurs: in some tissues differentiated cells are not replaced, while in others they die but are continuously replaced by new cells generated from stem cells.

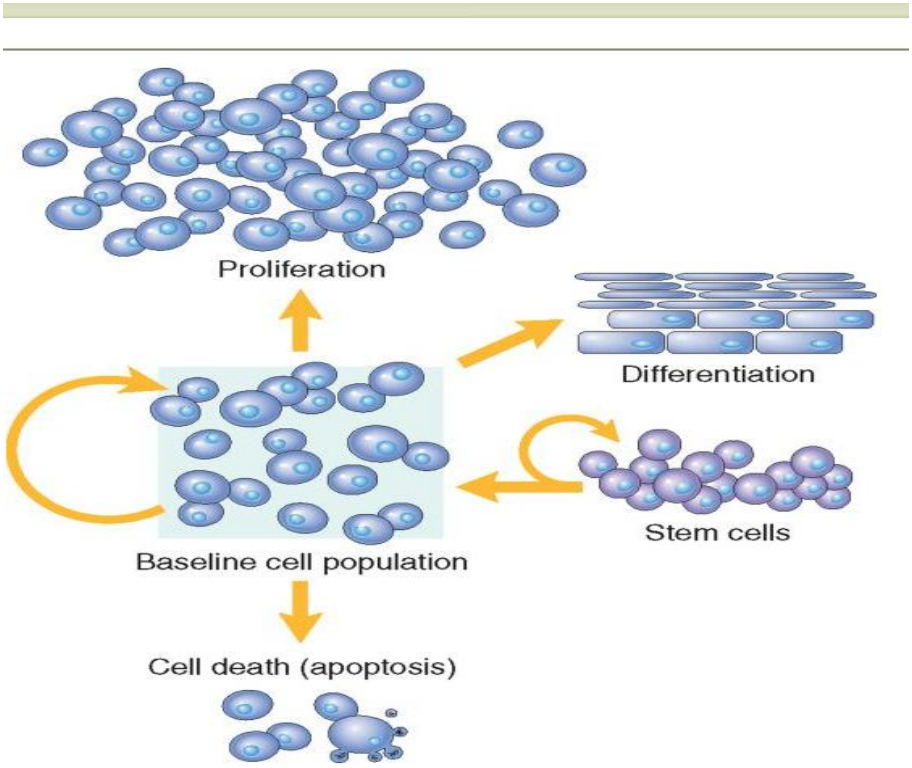


FIGURE 18. Mechanisms regulating cell populations. Cell numbers can be altered by increased or decreased rates of stem cell input, cell death due to apoptosis, or changes in the rates of proliferation or differentiation. *(Modified from McCarthy NJ et al: Apoptosis in the development of the immune system: growth factors, clonal selection and bcl-2. Cancer Metastasis Rev 11:157, 1992.)*

2.0 OBJECTIVES. At the end of this unit, you should be able to:

- Give an overview on the control of normal cell proliferation and tissue growth.
- Describe the cell cycle and mention factors regulating cell replication.
- Define and describe adaptations and other abnormalities of cellular growth and differentiation.

3.0 MAIN CONTENTS.

3.1 Control of Normal Cell Proliferation and Tissue Growth.

Cell proliferation can be stimulated by *physiologic and pathologic conditions*. The proliferation of endometrial cells under estrogen stimulation during the menstrual cycle and the thyroid-stimulating hormone–mediated replication of cells of the thyroid that enlarges the gland during pregnancy are examples of physiologic proliferation. Physiologic stimuli may become excessive, creating pathologic conditions such as *nodular prostatic hyperplasia* resulting from dihydro-testosterone stimulation and the development of *nodular goiters in the thyroid* as a consequence of increased serum levels of thyroid-stimulating hormone.

Cell proliferation is largely controlled by signals (soluble or contact-dependent) from the microenvironment that either stimulate or inhibit proliferation. *An excess of stimulators or a deficiency of inhibitors leads to net growth and, in the case of cancer, uncontrolled growth.*

Tissue proliferative activity: *The tissues of the body are divided into three groups on the basis of the proliferative activity of their cells:* This time-honored classification should be interpreted in the light of recent findings on stem cells and the reprogramming of cell differentiation.

- *Continuously dividing (labile tissues),*
- *Quiescent (stable tissues), and*
- *Nondividing (permanent tissues).*

C*ontinuously dividing tissues* cells proliferate throughout life, replacing those that are destroyed. These tissues include surface epithelia, such as stratified squamous epithelia of the skin, oral cavity, vagina, and cervix; the lining mucosa of all the excretory ducts of the glands of the body (e.g., salivary glands, pancreas, biliary tract); the columnar epithelium of the GI tract and uterus; the transitional epithelium of the urinary tract, and cells of the bone marrow and hematopoietic tissues. In most of these tissues mature cells are derived from adult *stem cells*, which have a tremendous capacity to proliferate and whose progeny may differentiate into several kinds of cells.

Quiescent tissues normally have a low level of replication; however, cells from these tissues can undergo rapid division in response to stimuli and are thus capable of reconstituting the tissue of origin. In this category are the parenchymal cells of liver, (as earlier described), kidneys, and pancreas; mesenchymal cells such as fibroblasts and smooth muscle; vascular endothelial cells; and lymphocytes and other leukocytes. The regenerative capacity of stable cells is best exemplified by the ability of the liver to regenerate after partial hepatectomy and after acute chemical injury.

Nondividing tissues contain cells that have left the cell cycle and cannot undergo mitotic division in postnatal life. To this group belong neurons and skeletal and cardiac muscle cells. If *neurons* in the central nervous system are destroyed, the tissue is generally replaced by the proliferation of the central nervous system–supportive elements, the glial cells.

Stem cells . Research on stem cells is at the forefront of modern-day biomedical investigation and stands at the core of a new field called *regenerative medicine*. The enthusiasm created by stem cell research derives from findings that challenge established views about cell differentiation, and from the hope that stem cells may one day be used to repair damaged human tissues, such as heart, brain, liver, and skeletal muscle.

3.1 Cell cycle and the Regulation of Cell Replication.

Cell proliferation is a tightly regulated process that involves a large number of molecules and interrelated pathways. To understand how cells proliferate during regeneration and repair, it is useful to summarize the key features of the normal cell cycle and its regulation.

The replication of cells is stimulated by growth factors or by signaling from ECM components through integrins. To achieve DNA replication and division, the cell goes through a tightly controlled sequence of events known as the *cell cycle. The cell cycle consists of* G_1 *(presynthetic), S (DNA synthesis),* G_2 *(premitotic), and M (mitotic) phases. Quiescent cells that have not entered the cell cycle are in the* G_0 *state* (Figure 19). Each cell cycle phase is dependent on the proper activation and completion of the previous one, and the cycle stops at a place at which an essential gene function is deficient.

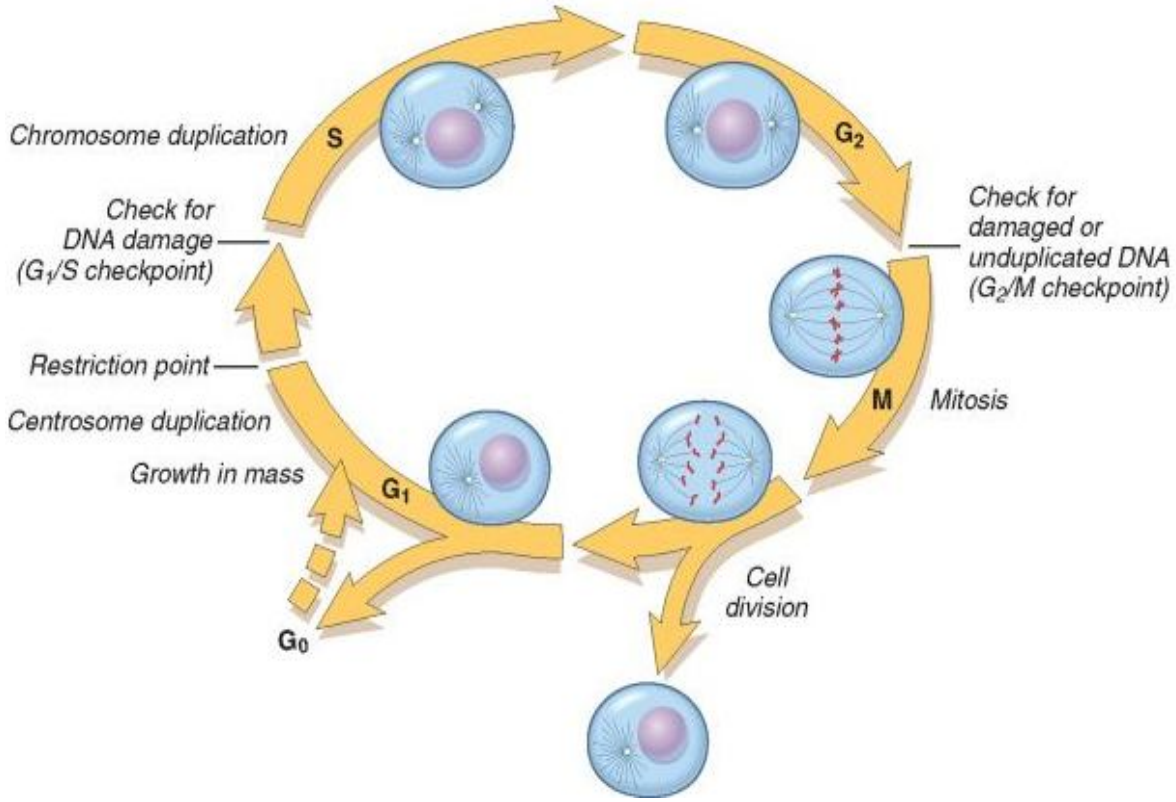


FIGURE 19. Cell cycle landmarks. The figure shows the cell cycle phases (G_0, G_1, G_2, S, and M), the location of the G_1 restriction point, and the G_1/S and G_2/M cell cycle checkpoints. Cells from labile tissues such as the epidermis and the GI tract may cycle continuously; stable cells such as hepatocytes are quiescent but can enter the cell cycle; permanent cells such as neurons and cardiac myocytes have lost the capacity to proliferate. *(Modified from Pollard TD, Earnshaw WC: Cell Biology. Philadelphia, Saunders, 2002.)*

3.2.1 Growth factors:

The proliferation of many cell types is driven by polypeptides known as growth factors. These factors, which can have restricted or multiple cell targets, may also promote cell survival, locomotion, contractility, differentiation, and angiogenesis, activities that may be as important as their growth-promoting effects.

TABLE 9. Growth Factors and Cytokines Involved in Regeneration and Wound Healing

Growth Factor	Symbol	Source	Functions
Epidermal growth α	EGF	Platelets, macrophages, saliva, urine, milk, plasma	Mitogenic for keratinocytes and fibroblasts; stimulates keratinocyte migration and granulation tissue formation
Transforming growth factor α	TGF-α	Macrophages, T lymphocytes, keratinocytes, and many tissues	Similar to EGF; stimulates replication of hepatocytes and most epithelial cells
Heparin-binding EGF	HB-EGF	Macrophages, mesenchymal cells	Keratinocyte replication
Hepatocyte growth factor/scatter factor	HGF	Mesenchymal cells	Enhances proliferation of hepatocytes, epithelial cells, and endothelial cells; increases cell motility, keratinocyte replication
Vascular endothelial cell growth factor (isoforms A, B, C, D)	VEGF	Many types of cells	Increases vascular permeability; mitogenic for endothelial cells (see Table 3-3); angiogenesis
Platelet-derived growth factor (isoforms A, B, C, D)	PDGF	Platelets, macrophages, endothelial cells, keratinocytes, smooth muscle cells	Chemotactic for PMNs, macrophages, fibroblasts, and smooth muscle cells; activates PMNs, macrophages, and fibroblasts; mitogenic for fibroblasts, endothelial cells, and smooth muscle cells; stimulates production of MMPs, fibronectin, and HA; stimulates angiogenesis and wound contraction
Fibroblast growth factor 1 (acidic), 2 (basic), and family	FGF	Macrophages, mast cells, T lymphocytes, endothelial cells, fibroblasts	Chemotactic for fibroblasts; mitogenic for fibroblasts and keratinocytes; stimulates keratinocyte migration, angiogenesis, wound contraction, and matrix deposition
Transforming growth factor β (isoforms 1,	TGF-β	Platelets, T lymphocytes,	Chemotactic for PMNs, macrophages, lymphocytes, fibroblasts, and smooth

2, 3); other members of the family are BMPs and activin		macrophages, endothelial cells, keratinocytes, smooth muscle cells, fibroblasts	muscle cells; stimulates TIMP synthesis, angiogenesis, and fibroplasia; inhibits production of MMPs and keratinocyte proliferation
Keratinocyte growth factor (also called FGF-7)	KGF	Fibroblasts	Stimulates keratinocyte migration, proliferation, and differentiation
Tumor necrosis factor	TNF	Macrophages, mast cells, T lymphocytes	Activates macrophages; regulates other cytokines; multiple functions

Modified from Schwartz SI: Principles of Surgery. New York, McGraw-Hill, 1999.

BMP, bone morphogenetic proteins; HA, hyaluronate; MMPs, matrix metalloproteinases; PMNs, polymorphonuclear leukocytes; TIMP, tissue inhibitor of MMP.

3.3. Abnormalities of Cellular Growth and Differentiation

Adaptations are reversible changes in the size, number, phenotype, metabolic activity, or functions of cells in response to changes in their environment. Such adaptations may take several distinct forms.

3.3.1 Hypertrophy.

This 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. Cells capable of division may respond to stress by undergoing both hyperplasia (described below) and hypertrophy, whereas in nondividing cells (e.g., myocardial fibers) increased tissue mass is due to hypertrophy. In many organs hypertrophy and hyperplasia may coexist and contribute to increased size.

Hypertrophy can be *physiologic* or *pathologic* and is caused by increased functional demand or by stimulation by hormones and growth factors.

Hypertrophy is the result of increased production of cellular proteins. The striated muscle cells in the heart and skeletal muscles have only a limited capacity for division, and respond to increased metabolic demands mainly by undergoing hypertrophy. *The most common stimulus for hypertrophy of muscle is increased workload*. For example, the bulging muscles of bodybuilders engaged in “pumping iron” result from an increase in size of the individual muscle fibers in response to increased demand. In the heart, the stimulus for hypertrophy is usually chronic hemodynamic overload, resulting from either hypertension or faulty valves.

3.3.2 Hyperplasia

This is an increase in the number of cells in an organ or tissue, usually resulting in increased mass of the organ or tissue. Although hyperplasia and hypertrophy are distinct processes, frequently they occur together, and they may be triggered by the same external stimulus. Hyperplasia takes place if the cell population is capable of dividing, and thus increasing the number of cells. *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*. Hyperplasia can be physiologic or pathologic.

Physiologic hyperplasia can be divided into: (1) *hormonal hyperplasia*, which increases the functional capacity of a tissue when needed (exemplified by breast tissue growth at puberty and during pregnancy) and (2) *compensatory hyperplasia* which increases tissue mass after damage or partial resection (e.g. liver tissue, as earlier mentioned).

Pathologic Hyperplasia are caused by *excesses of hormones or growth factors* acting on target cells. Endometrial hyperplasia is an example of abnormal hormone-induced hyperplasia. Although these forms of hyperplasia are abnormal, the process remains controlled because there are no mutations in genes that regulate cell division, and the hyperplasia regresses if the hormonal stimulation is eliminated. As is discussed in Chapter 7 , in cancer the growth control mechanisms become dysregulated or ineffective because of genetic aberrations, resulting in unrestrained proliferation. *Thus, hyperplasia is distinct from cancer, but pathologic hyperplasia constitutes a fertile soil in which cancerous proliferation may eventually arise*. For instance, patients with hyperplasia of the endometrium are at increased risk for developing endometrial cancer.

3.3.3 Atrophy.

Atrophy is reduced size of an organ or tissue resulting from a decrease in cell size and number. Atrophy results from decreased protein synthesis and increased protein degradation in cells. Atrophy can be physiologic or pathologic.

Physiologic atrophy is common during normal development. Some embryonic structures, such as the notochord and thyroglossal duct, undergo atrophy during fetal development. The uterus also decreases in size shortly after parturition.

Pathologic atrophy depends on the underlying cause and can be local or generalized. The common causes of atrophy are the following:

- *Decreased workload (atrophy of disuse)*. When a fractured bone is immobilized in a plaster cast or when a patient is restricted to complete bedrest, skeletal muscle atrophy rapidly ensues. The initial decrease in cell size is reversible once activity is resumed.
- *Loss of innervation (denervation atrophy)*.

- *Diminished blood supply.* In late adult life, the brain may undergo progressive atrophy, mainly because of reduced blood supply as a result of atherosclerosis (Fig. 20B). This is called *senile atrophy*; it also affects the heart.

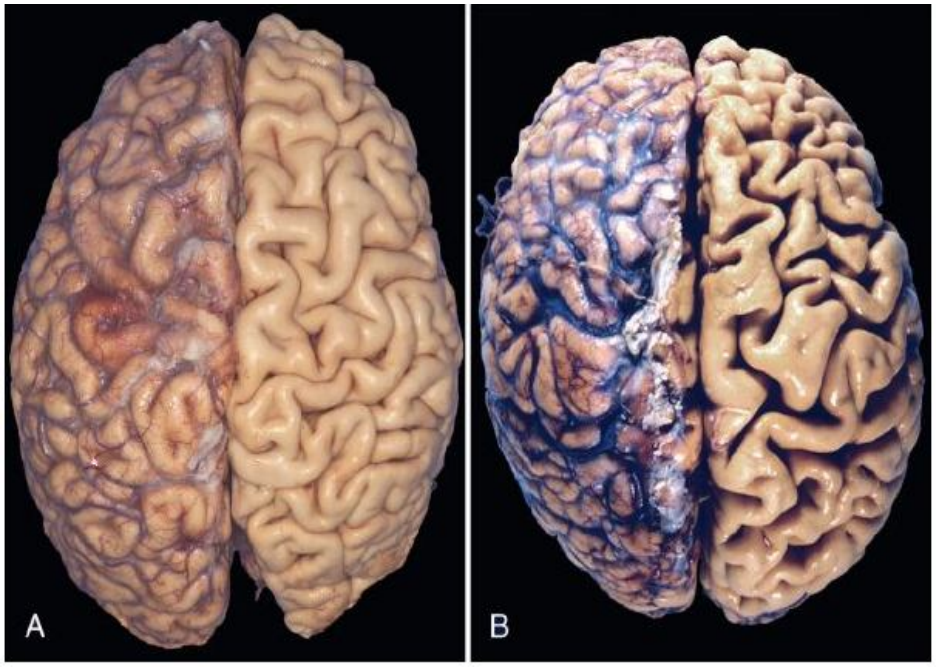


FIGURE 20. Atrophy. A, Normal brain of a young adult. B, Atrophy of the brain in an 82-year-old male with atherosclerotic cerebrovascular disease, resulting in reduced blood supply. Note that loss of brain substance narrows the gyri and widens the sulci. The meninges have been stripped from the right half of each specimen to reveal the surface of the brain.

- *Inadequate nutrition*. Profound protein-calorie malnutrition (marasmus) is associated with the use of skeletal muscle as a source of energy after other reserves such as adipose stores have been depleted.
- *Loss of endocrine stimulation, e.g* The loss of estrogen stimulation after menopause results in physiologic atrophy of the endometrium, vaginal epithelium, and the breast.
- *Pressure*. Tissue compression for any length of time can cause atrophy. An enlarging benign tumor can cause atrophy in the surrounding uninvolved tissues. Atrophy in this setting is probably the result of ischemic changes caused by compromise of the blood supply by the pressure exerted by the expanding mass.

3.3.4 Differentiation and Anaplasia:

Differentiation refers to the extent to which neoplastic parenchymal cells resemble the corresponding normal parenchymal cells, both morphologically and functionally; lack of differentiation is called anaplasia.

Malignant neoplasms that are composed of poorly differentiated cells are said to be *anaplastic. Lack of differentiation, or anaplasia, is considered a hallmark of malignancy.* The term *anaplasia* literally means "to form backward," implying a reversal of differentiation to a more primitive level. It is believed, however, that most

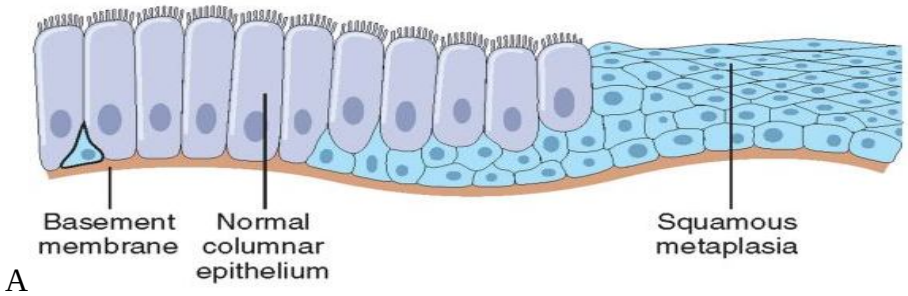
cancers do not represent "reverse differentiation" of mature normal cells but, in fact, arise from less mature cells with "stem-cell-like" properties, such as tissue stem cells

3.3.5 Metaplasia

Metaplasia is a reversible change in which one differentiated cell type (epithelial or mesenchymal) is replaced by another cell type. It may represent an adaptive substitution of cells that are sensitive to stress by cell types better able to withstand the adverse environment.

The most common epithelial metaplasia is *columnar* to *squamous* (Figure 21), as occurs in the respiratory tract in response to chronic irritation. In the habitual cigarette smoker, the normal ciliated columnar epithelial cells of the trachea and bronchi are often replaced by stratified squamous epithelial cells. Stones in the excretory ducts of the salivary glands, pancreas, or bile ducts may also 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. In all these instances the more rugged stratified squamous epithelium is able to survive under circumstances in which the more fragile specialized columnar epithelium might have succumbed.

However, the change to metaplastic squamous cells comes with a price. In the respiratory tract, for example, although the epithelial lining becomes tough, important mechanisms of protection against infection—mucus secretion and the ciliary action of the columnar epithelium—are lost. Thus, epithelial metaplasia is a double-edged sword and, in most circumstances, represents an undesirable change. Moreover, *the influences that predispose to metaplasia, if persistent, may initiate malignant transformation in metaplastic epithelium*. Thus, a common form of cancer in the respiratory tract is composed of squamous cells, which arise in areas of metaplasia of the normal columnar epithelium into squamous epithelium.



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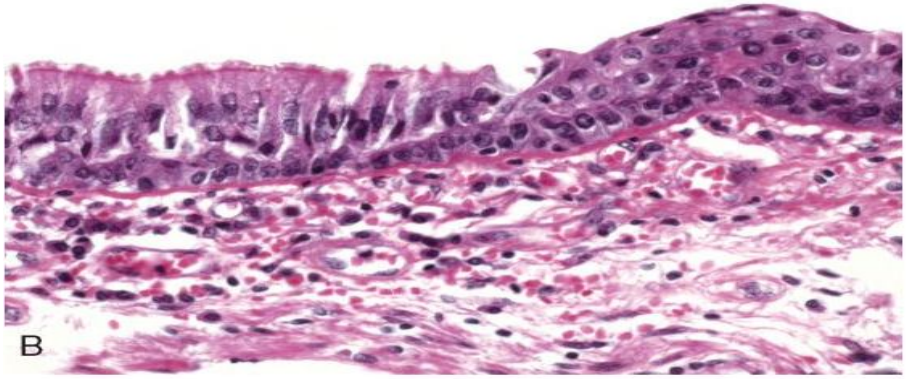

FIGURE 21. *Metaplasia of columnar to squamous epithelium. A, Schematic diagram. B, Metaplasia of columnar epithelium (left) to squamous epithelium (right) in a bronchus.*

3.3.6. Dysplasia

This literally means disordered growth. Dysplasia often occurs in metaplastic epithelium, but not all metaplastic epithelium is also dysplastic. Dysplasia is encountered principally in epithelia, and it is characterized by a constellation of changes that *include a loss in the uniformity of the individual cells as well as a loss in their architectural orientation*. Dysplastic cells exhibit considerable pleomorphism and often contain large hyperchromatic nuclei with a high nuclearto-cytoplasmic ratio. The architecture of the tissue may be disorderly. For example,in squamous epithelium the usual progressive maturation of tall cells in the basal layer to flattened squames on the surface may be lost and replaced by a scrambling of dark basal-appearing cells throughout the epithelium. Mitotic figures are more abundant than usual, although almost invariably they have a normal configuration. Frequently, however, the mitoses appear in abnormal locations within the epithelium. For example, in dysplastic stratified squamous epithelium, mitoses are not confined to the basal layers but instead may appear at alllevels, including surface cells. When dysplastic changes are marked and involve the entire thickness of the epithelium but the lesion remains confined by the basement membrane, it is considered a preinvasive neoplasm and is referred to as *carcinoma in situ*. Once the tumor cells breach the basement membrane, the tumor is said to be *invasive*. Dysplastic changes are often found adjacent to foci of invasive carcinoma, and in some situations, such as in long-term cigarette smokers and persons with Barrett esophagus, severe epithelial dysplasia frequently antedates the appearance of cancer. However, *dysplasia does not necessarily progress to cancer*.

4.0 CONCLUSION

This unit shows that the characterization of tissue growth and differentiation helps to determine, to a large extent the potential for carcinogenesis.

5.0. SUMMARY. This unit teaches us about:

- The factors involved in the control of normal cell proliferation and tissue growth
- The cell cycle and the regulation of cell replication
- The numerous growth factors involved in cell replication.
- Abnormalities of cellular growth and differentiation.

6.0 TUTOR-MARKED ASSIGNMENT.

List and describe the three groups of body tissues.

List ten growth factors that you know. List their functions.

With the aid of an illustration/diagram, briefly describe the cell cycle.

Briefly describe the abnormalities of cellular growth and differentiation that you know.

7.0 REFERENCES:

- **Robbins and Cotran Pathologic Basis of Diseases. Eight edition.**
- **Essentials of Pathology. By Emanuel Rubin. Third edition.**

UNIT 2: NEOPLASIA.

CONTENTS

1.0 INTRODUCTION.

Cancer is the second leading cause of death in the United States; only cardiovascular diseases exact a higher toll. Even more agonizing than the mortality rate is the emotional and physical suffering inflicted by neoplasms. Patients and the public often ask, “When will there be a cure for cancer?” The answer to this simple question is difficult, because cancer is not one disease but many disorders that share a profound growth dysregulation. Some cancers, such as Hodgkin lymphoma, are curable, whereas others, such as pancreatic adenocarcinoma, have a high mortality.

The only hope for controlling cancer lies in learning more about its cause and pathogenesis, and great strides have been made in understanding its molecular basis. Indeed, some good news has emerged: cancer mortality for both men and women in the United States declined during the last decade of the twentieth century and has continued its downward course in the 21st.

The role of the nurse clinician in the management of a cancer patient cannot be overemphasized! A clear understanding of the progression of the disease and the sensitivity to the need of the patient carried on the platform of empathy, is a sine qua none.

2.0 O**BJECTIVES**. At the end of this unit, you should be able to:

1) Define the term neoplasm and other synonyms.
2) Differentiate between benign and malignant tumours.
3) Describe the molecular basis of cancer.
4) Discuss the impact of oncogens, tumour-suppressor genes and failure of apoptosis in carcinogenesis
5) Enumerate carcinogenic agents and their roles in carcinogenesis.
6) Describe host defense mechanisms against cancer.
7) Discuss the clinical aspects of neoplasia.

3.0 MAIN CONTENTS.

3.1 Nomenclature.

Neoplasia means "new growth," and a new growth is called a *neoplasm. Tumour* originally applied to the swelling caused by inflammation, but the non-neoplastic usage of *tumor* has almost vanished; thus, the term is now equated with neoplasm. *Oncology* (Greek *oncos* = tumor) is the study of tumors or neoplasms.

According to the eminent British oncologist, Willis, *"a neoplasm is an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissues and persists in the same excessive manner after cessation of the stimuli which evoked the change."*

The persistence of tumors, even after the inciting stimulus is gone, results from *genetic alterations that are passed down to the progeny of the tumor cells. These genetic changes allow excessive and unregulated proliferation that becomes autonomous (independent of physiologic growth stimuli),* although tumors generally remain dependent on the host for their nutrition and blood supply.

A tumor is said to be benign when its microscopic and gross characteristics are considered relatively innocent, implying that it will remain localized, it cannot spread to other sites, and it is generally amenable to local surgical removal; the patient generally survives. It should be noted, however, that benign tumors can produce more than localized lumps, and

sometimes they are responsible for serious disease.

Malignant tumors are collectively referred to as *cancers*, derived from the Latin word for *crab*, because they adhere to any part that they seize on in an obstinate manner, similar to a crab. *Malignant*, as applied to a neoplasm, implies that the lesion can invade and destroy adjacent structures and spread to distant sites (metastasize) to cause death. Not all cancers pursue so deadly a course. Some are discovered early and are treated successfully, but the designation *malignant* always raises a red flag

3.2 Characteristics of benign and malignant tumours.

TABLE 10. Comparisons between Benign and Malignant Tumors

Characteristics	Benign	Malignant
Differentiation/anaplasia	Well differentiated; structure sometimes typical of tissue of origin	Some lack of differentiation with anaplasia; structure often atypical
Rate of growth	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
Local invasion	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
Metastasis	Absent	Frequently present; the larger and more undifferentiated the primary, the more likely are metastases

Example

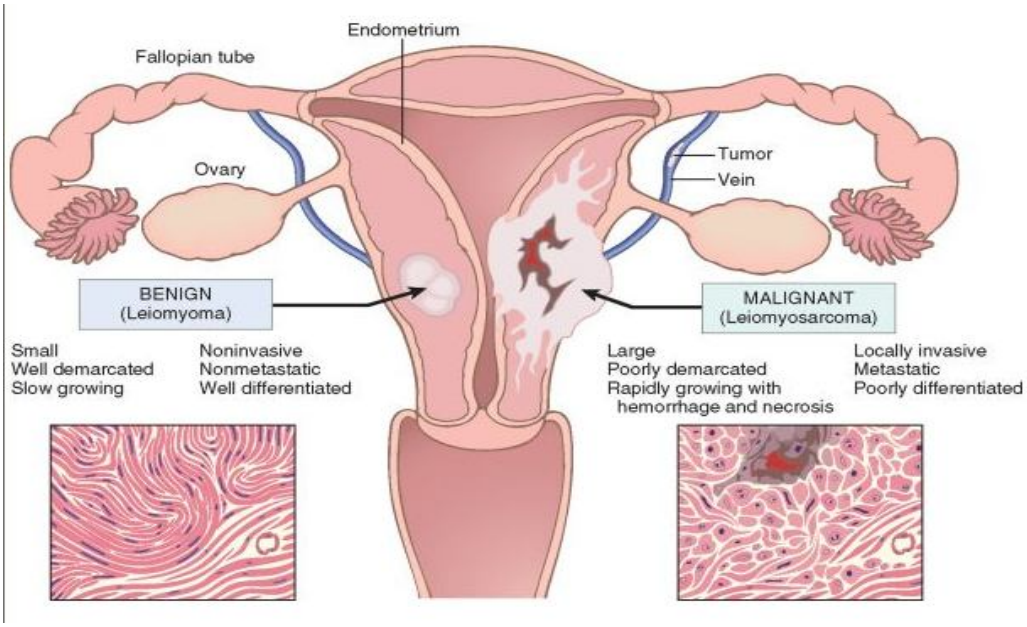

FIGURE 22 Comparison between a benign tumor of the myometrium (leiomyoma) and a malignant tumor of the same origin (leiomyosarcoma).

3.3 Molecular basis of cancer

3.3.1 Principles involved in the molecular basis of cancer.

1) *Nonlethal genetic damage lies at the heart of carcinogenesis*. Such genetic damage (or mutation) may be acquired by the action of environmental agents, such as chemicals, radiation, or viruses, or it may be inherited in the germ line. The term *environmental*, used in this context, involves any acquired defect caused by exogenous agents or endogenous products of cell metabolism.
2) *A tumour is formed by the clonal expansion of a single precursor cell that has incurred genetic damage (i.e., tumors are monoclonal).*
3) *Four classes of normal regulatory genes are the principal targets of genetic damage:*
    i. *the growth-promoting proto-oncogenes,*
    ii. *the growth-inhibiting tumour suppressor genes,*
    iii. *genes that regulate cell death (apoptosis),*
    iv. *genes involved in DNA repair.*
4) *Carcinogenesis is a multistep process at both the phenotypic and the genetic levels, resulting from the accumulation of multiple mutations.*

3.3.2 Essential alterations for malignant *programmed* transformation.

Over the past two decades, hundreds of cancer-associated genes have been discovered. Some, such as *p53*, are mutated in many different cancers; others, such as *ABL1*, are affected only in one or few. Each of the cancer-associated genes has a specific function, the dysregulation of which contributes to the origin or progression of malignancy. It is traditional to describe cancer-associated genes on the basis of their presumed function. It is beneficial, however, to consider cancer- related genes in the context of *seven fundamental changes in cell physiology that together determine malignant phenotype*. (Another important change for tumour development is *escape from immune attack).*

The seven key changes are the following:

- *Self-sufficiency in growth signals*: Tumours have the capacity to proliferate without external stimuli, usually as a consequence of oncogens activation.
- *Insensitivity to growth-inhibitory signals*: Tumours may not respond to molecules that are inhibitory to the proliferation of normal cells such as transforming growth factor β (TGF-β) and direct inhibitors of cyclin-dependent kinases (CDKIs).
- *Evasion of apoptosis*: Tumours may be resistant to programmed cell death, as a consequence of inactivation of *p53* or activation of anti-apoptotic genes.
- *Limitless replicative potential*: Tumour cells have unrestricted proliferative capacity, avoiding cellular senescence and mitotic catastrophe.
- *Sustained angiogenesis*: Tumour cells, like normal cells, are not able to grow without formation of a vascular supply to bring nutrients and oxygen and remove waste products. Hence, tumors must induce angiogenesis.
- *Ability to invade and metastasize*: Tumour metastases are the cause of the vast majority of cancer deaths and depend on processes that are intrinsic to the cell or are initiated by signals from the tissue environment.
- *Defects in DNA repair*: Tumours may fail to repair DNA damage caused by carcinogens or incurred during unregulated cellular proliferation, leading to genomic instability and mutations in proto-oncogenes and tumor suppressor genes.

Mutations in one or more genes that regulate these cellular traits are seen in every cancer. However, the precise genetic pathways that give rise to these attributes differ between individual cancers, even within the same organ. It is widely believed that the occurrence of mutations in cancer-related genes is conditioned by the robustness of the DNA-repair machinery, as well as protective mechanisms such as apoptosis and senescence that prevent the proliferation of cells with damaged DNA. Indeed, recent studies in a variety of human tumors, such as melanoma and prostate adenocarcinoma, have shown that oncogen-induced senescence, wherein mutation of a proto-oncogene drives cells into senescence rather than proliferation, is an important barrier to

carcinogenesis.

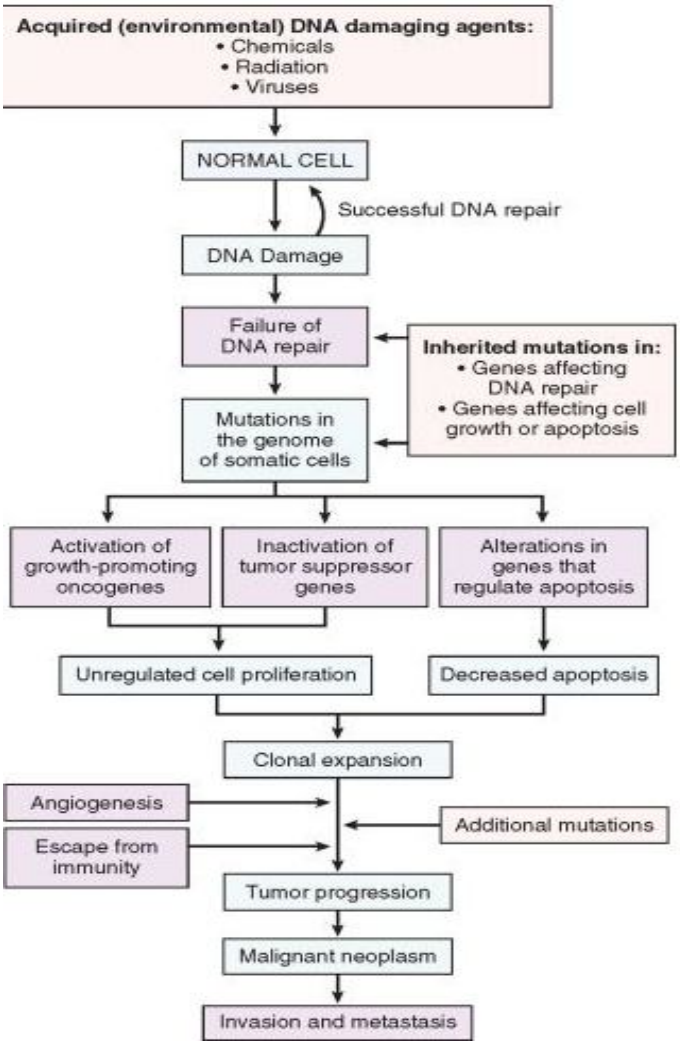

FIGURE 23. Flowchart depicting a simplified scheme of the molecular basis of cancer.

SELF-SUFFICIENCY IN GROWTH SIGNALS: ONCOGENES

Genes that promote autonomous cell growth in cancer cells are called *oncogenes*, and their unmutated cellular counterparts are called *proto-oncogenes*. Oncogenes are created by mutations in proto-oncogenes and are characterized by the ability to promote cell growth in the absence of normal growth-promoting signals. Their products, called *oncoproteins*, resemble the normal products of proto-oncogenes except that oncoproteins are often devoid of important internal regulatory elements, and their production in the transformed cells does not depend on growth factors or other external signals.

Examples of oncogens.

Table 11. Selected Oncogenes, Their Mode of Activation, and Associated Human Tumors

Category	Proto-oncogene	Mode of Activation	Associated Human Tumor
GROWTH FACTORS			
PDGF-β chain	*SIS* (official name *PBGFB*)	Over expression	Astrocytoma
			Osteosarcoma
Fibroblast growth factors	*HST1*	Over expression	Stomach cancer
	INT2 (official name *FGF3*)	Amplification	Bladder cancer
			Breast cancer
			Melanoma
TGF-α	*TGFA*	Over expression	Astrocytomas
			Hepatocellular carcinomas
HGF	*HGF*	Over expression	Thyroid cancer
GROWTH FACTOR RECEPTORS			
EGF-receptor family	*ERBB1* (*EGFR*), *ERRB2*	Over expression	Squamous cell carcinoma of lung, gliomas
FMS-like tyrosine kinase 3	*FLT3*	Amplification	Breast and ovarian cancers
Receptor for neurotrophic factors	*RET*	Point mutation	Leukemia
		Point mutation	Multiple endocrine neoplasia 2A and B, familial medullary thyroid carcinomas
PDGF receptor	*PDGFRB*	Over expression, translocation	Gliomas, leukemias
Receptor for stem cell (steel) factor	*KIT*	Point mutation	Gastrointestinal stromal tumours, seminomas, leukemias
PROTEINS INVOLVED IN SIGNAL TRANSDUCTION			
GTP-binding	*KRAS*	Point mutation	Colon, lung, and pancreatic tumors
	HRAS	Point mutation	Bladder and kidney tumors

	NRAS	Point mutation	Melanomas, hematologic malignancies
Nonreceptor tyrosine kinase	*ABL*	Translocation	Chronic myeloid leukemia
			Acute lymphoblastic leukemia
RAS signal transduction	*BRAF*	Point mutation	Melanomas
WNT signal transduction	β-catenin	Point mutation	Hepatoblastomas, hepatocellular carcinoma
		Over expression	
NUCLEAR-REGULATORY PROTEINS			
Transcriptional activators	C-*MYC*	Translocation	Burkitt lymphoma
	N-*MYC*	Amplification	Neuroblastoma, small-cell carcinoma of lung
	L-*MYC*	Amplification	Small-cell carcinoma of lung
CELL CYCLE REGULATORS			
Cyclins	Cyclin D	Translocation	Mantle cell lymphoma
		Amplification	Breast and esophageal cancers
	Cyclin E	Over expression	Breast cancer
Cyclin-dependent kinase	*CDK4*	Amplification or point mutation	Glioblastoma, melanoma, sarcoma

Insensitivity to growth inhibition and escape from senescence: tumour suppressor genes.

Failure of growth inhibition is one of the fundamental alterations in the process of carcinogenesis. Whereas oncogenes drive the proliferation of cells, the products of *tumour suppressor genes apply brakes to cell proliferation*. It has become apparent that the tumor suppressor proteins form a network of checkpoints that prevent uncontrolled growth. Many tumor suppressors, such as RB and p53, are part of a regulatory network that recognizes genotoxic stress from any source, and responds by shutting down proliferation.

Table 12. Selected Tumor Suppressor Genes Involved in Human Neoplasms

Subcellular Locations	Gene	Function	Tumors Associated with Somatic Mutations	Tumors Assocated 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, pancreas; melanoma	Familial adenomatous polyposis 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	Pancreatic, breast, and esophageal	Malignant melanoma

		of cyclindependent kinases	cancers	
	BRCA1 and *BRCA2*	DNA repair	Unknown	Carcinomas of female breast and ovary; carcinomas of male breast

PI3 kinase, phosphatidylinositol 3-kinase.

Evasion of Apoptosis

Accumulation of neoplastic cells may result not only from activation of growth-promoting oncogenes or inactivation of growth-suppressing tumor suppressor genes, but also from mutations in the genes that regulate apoptosis. Thus, apoptosis represents a barrier that must be surmounted for cancer to occur. In the adult, cell death by apoptosis is a physiologic response to several pathologic conditions that might contribute to malignancy if the cells remained viable. A cell with genomic injury can be induced to die, preventing the accumulation of cells with mutations. A variety of signals, ranging from DNA damage to loss of adhesion to the basement membrane (termed *anoikis*), can trigger apoptosis. A large family of genes that regulate apoptosis has been identified. Before we can understand how tumor cells evade apoptosis, it is essential to review briefly the biochemical pathways to apoptosis.

Angiogenesis

Even with all the genetic abnormalities discussed above, solid tumors cannot enlarge beyond 1 to 2 mm in diameter unless they are vascularized. Like normal tissues, tumors require delivery of oxygen and nutrients and removal of waste products; presumably the 1- to 2-mm zone represents the maximal distance across which oxygen, nutrients, and waste can diffuse from blood vessels. Cancer cells can stimulate neo-angiogenesis, during which new vessels sprout from previously existing capillaries, or, in some cases, vasculogenesis, in which endothelial cells are recruited from the bone marrow. Tumour vasculature is abnormal, however. The vessels are leaky and dilated, and have a haphazard pattern of connection. Neovascularization has a dual effect on tumour growth: perfusion supplies needed nutrients and oxygen, and newly formed endothelial cells stimulate the growth of adjacent tumour cells by secreting growth factors, such as insulin-like growth factors (IGFs), PDGF, and granulocyte-macrophage colony-stimulating factor.

Angiogenesis is required not only for continued tumour growth but also for access to the vasculature and hence for metastasis. *Angiogenesis is thus a necessary biologic correlate of malignancy*.

I

Invasion and Metastasis

Invasion and metastasis are biologic hallmarks of malignant tumours. They are the major cause of cancer-related morbidity and mortality and hence are the subjects of intense scrutiny. Studies in mice and humans reveal that although millions of cells are released into the circulation each day from a primary tumour, only a few metastases are produced. Indeed, tumour cells can be frequently detected in the blood and marrow of patients with breast cancer who have not, and do not ever, develop gross metastatic disease. Why is the metastatic process so inefficient? Each step in the process is subject to a multitude of controls; hence, at any point in the sequence the breakaway cell may not survive.

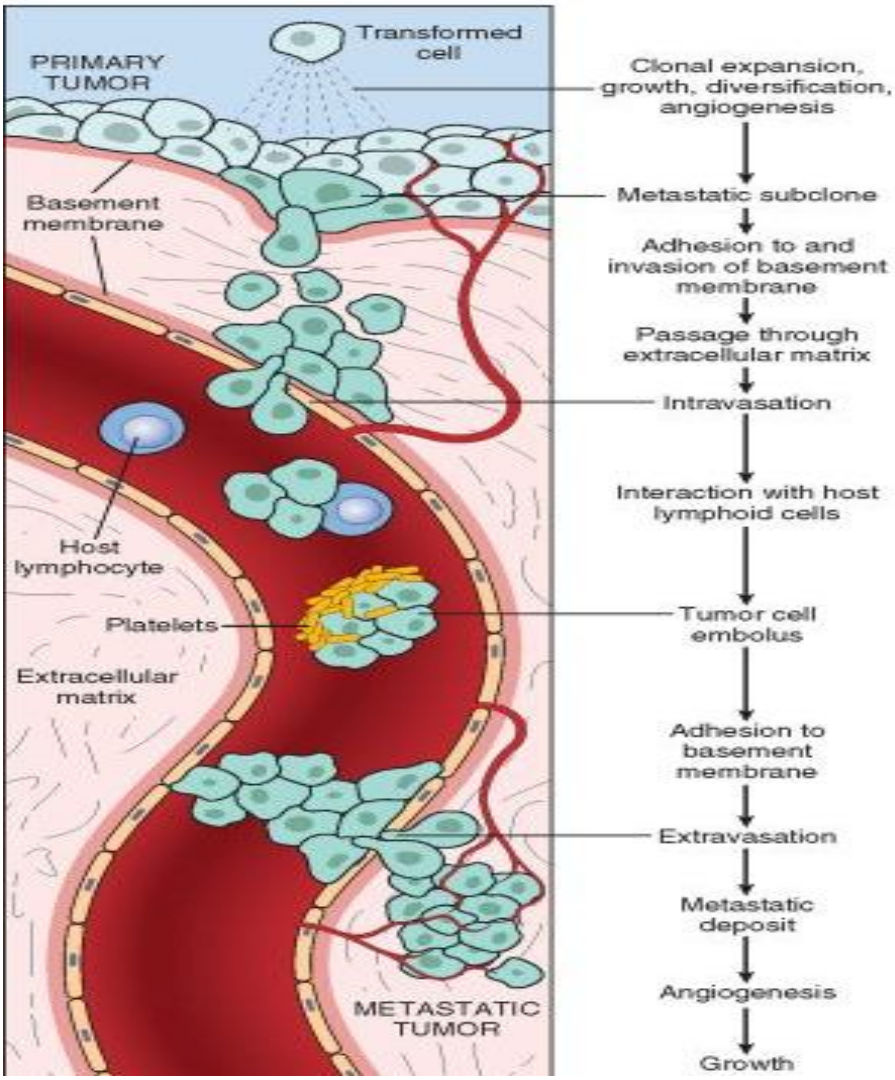

FIGURE 24 The metastatic cascade. Sequential steps involved in the hematogenous spread of a tumor.

3.4 Carcinogenic Agents and Their Cellular Interactions

More than 200 years ago the London surgeon Sir Percival Pott correctly attributed scrotal skin cancer in chimney sweeps to chronic exposure to soot. Based on this observation, the Danish Chimney Sweeps Guild ruled that its members must bathe daily. No public health measure since that time has achieved so much in the control of a form of cancer.

Chemical carcinogenesis

Some of the major agents are presented in Table 13. bellow.

TABLE 13. Major Chemical Carcinogens

DIRECT-ACTING CARCINOGENS
Alkylating Agents
β-Propiolactone Dimethyl sulfate Diepoxybutane Anticancer drugs (cyclophosphamide, chlorambucil, nitrosoureas, and others)
Acylating Agents
1-Acetyl-imidazole Dimethylcarbamyl chloride
PROCARCINOGENS THAT REQUIRE METABOLIC ACTIVATION
Polycyclic and Heterocyclic Aromatic Hydrocarbons
Benz[*a*]anthracene Benzo[*a*]pyrene Dibenz[*a,h*]anthracene 3-Methylcholanthrene 7,12-Dimethylbenz[*a*]anthracene
Aromatic Amines, Amides, Azo Dyes
2-Naphthylamine (β-naphthylamine) Benzidine 2-Acetylaminofluorene

Dimethylaminoazobenzene (butter yellow)
Natural Plant and Microbial Products
Aflatoxin B_1
Griseofulvin Cycasin Safrole Betel nuts
Others
Nitrosamine and amides Vinyl chloride, nickel, chromium Insecticides, fungicides Polychlorinated biphenyls

Steps Involved in Chemical Carcinogenesis

As discussed earlier, carcinogenesis is a multistep process. This is most readily demonstrated in experimental models of chemical carcinogenesis, in which the stages of initiation and progression during cancer development were first described.[146] The classic experiments that allowed the distinction between initiation and promotion were performed on mouse skin and are outlined in Figure 7-41 . The following concepts relating to the initiation-promotion sequence have emerged from these experiments:

- *Initiation* results from exposure of cells to a sufficient dose of a carcinogenic agent (initiator); an initiated cell is altered, making it potentially capable of giving rise to a tumor (groups 2 and 3). *Initiation alone, however, is not sufficient for tumor formation* (group 1).
- *Initiation causes permanent DNA damage (mutations). It is therefore rapid and irreversible and has "memory."* This is illustrated by group 3, in which tumors were produced even if the application of the promoting agent was delayed for several months after a single application of the initiator.
- *Promoters can induce tumors in initiated cells, but they are nontumorigenic by themselves* (group 5). Furthermore, tumors do not result when the promoting agent is applied before, rather than after, the initiating agent (group 4). This indicates that, *in contrast to the effects of initiators, the cellular changes resulting from the application of promoters do not affect DNA directly and are reversible*. As discussed later, promoters enhance the proliferation of initiated cells, an effect that may contribute to the development of additional mutations in these cells. That the effects of promoters are

reversible is further documented in group 6, in which tumors failed to develop in initiated cells if the time between multiple applications of the promoter was sufficiently extended.

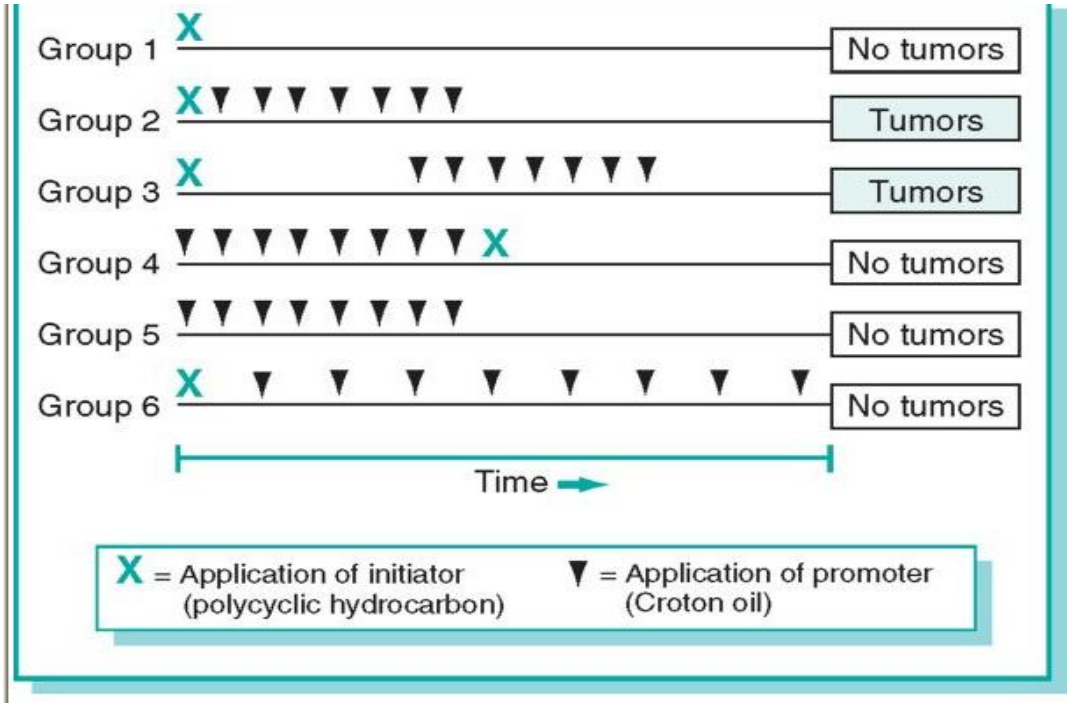

FIGURE **25**. Experiments demonstrating the initiation and promotion phases of carcinogenesis in mice. Group 2: application of promoter repeated at twice-weekly intervals for several months. Group 3: application of promoter delayed for several months and then applied twice weekly. Group 6: promoter applied at monthly intervals.

Direct-Acting Agents. They require no metabolic conversion to become carcinogenic. Most of them are weak carcinogens but are important because some are cancer chemotherapeutic drugs (e.g., Alkylating agents) that have successfully cured, controlled, or delayed recurrence of certain types of cancer (e.g., leukemia, lymphoma, and ovarian carcinoma), only to evoke later a second form of cancer, usually acute myeloid leukemia.

Indirect-Acting Agents. The designation *indirect-acting agent* refers to chemicals that require metabolic conversion to an *ultimate carcinogen* before they become active. Some of the most potent indirect chemical carcinogens—the polycyclic hydrocarbons—are present in fossil fuels. Others, for example, benzo[*a*]pyrene and other carcinogens, are formed in the high-temperature combustion of tobacco in cigarette smoking. *These products are implicated in the causation of lung cancer in cigarette smokers*. Polycyclic hydrocarbons may also be produced from animal fats during the process of broiling meats and are present in smoked meats and fish. The principal active products in many hydrocarbons are epoxides, which form covalent adducts (addition

products) with molecules in the cell, principally DNA, but also with RNA and proteins.

Radiation Carcinogenesis

Radiant energy, whether in the form of the UV rays of sunlight or as ionizing electromagnetic and particulate radiation, is a well-established carcinogen. UV light is clearly implicated in the causation of skin cancers, and ionizing radiation exposure from medical or occupational exposure, nuclear plant accidents, and atomic bomb detonations has produced a variety of cancers. Although the contribution of radiation to the total human burden of cancer is probably small, the well-known latency of damage caused by radiant energy and its cumulative effect require extremely long periods of observation and make it difficult to ascertain its full significance. An increased incidence of breast cancer has become apparent decades later among women exposed during childhood to atomic bomb tests.

Ultraviolet Rays

There is ample evidence from epidemiologic studies that *UV rays* derived from the sun cause an increased incidence of squamous cell carcinoma, basal cell carcinoma, and possibly melanoma of the skin. The degree of risk depends on the type of UV rays, the intensity of exposure, and the quantity of the light-absorbing "protective mantle" of melanin in the skin. Persons of European origin who have fair skin that repeatedly becomes sunburned but stalwartly refuses to tan and who live in locales receiving a great deal of sunlight (e.g., Queensland, Australia, close to the equator) have among the highest incidence of skin cancers (melanomas, squamous cell carcinomas, and basal cell carcinomas) in the world.

Ionizing Radiation

Electromagnetic (x-rays, γ rays) and particulate (α particles, β particles, protons, neutrons) radiations are all carcinogenic. The evidence is so voluminous that a few examples suffice. Many individuals pioneering the use of x-rays developed skin cancers. Miners of radioactive elements in central Europe and the Rocky Mountain region of the United States have a tenfold increased incidence of lung cancers compared to the rest of the population. Most telling is the follow-up of survivors of the atomic bombs dropped on Hiroshima and Nagasaki. Initially there was a marked increase in the incidence of leukemias—principally acute and chronic myelogenous leukemia—after an average latent period of about 7 years. Subsequently the incidence of many solid tumors with longer latent periods (e.g., breast, colon, thyroid, and lung) increased.

Microbial Carcinogenesis

Many RNA and DNA viruses have proved to be oncogenic in animals as disparate as frogs and primates. Despite intense scrutiny, however, only a few viruses have been linked with human cancer. Our discussion focuses on human oncogenic viruses as well as the emerging role of the bacterium *Helicobacter pylori* in gastric cancer.

Human T-Cell Leukemia Virus Type 1.

Although the study of animal retroviruses has provided spectacular insights into the molecular basis of cancer, only one human retrovirus, human T-cell leukemia virus type 1 (HTLV-1), is firmly implicated in the causation of cancer in humans.

HTLV-1 causes a form of T-cell leukemia/lymphoma that is endemic in certain parts of Japan and the Caribbean basin but is found sporadically elsewhere, including the United States. Similar to the human immunodeficiency virus, which causes acquired immunodeficiency syndrome (AIDS), HTLV-1 has tropism for CD4+ T cells, and hence this subset of T cells is the major target for neoplastic transformation.

Human Papillomavirus.

At least 70 genetically distinct types of HPV have been identified. Some types (e.g., 1, 2, 4, and 7) cause benign squamous papillomas (warts) in humans. By contrast, high-risk HPVs (e.g., types 16 and 18) have been implicated in the genesis of several cancers, particularly squamous cell carcinoma of the cervix and anogenital region. Thus, cervical cancer is a sexually transmitted disease, caused by transmission of HPV. In addition, at least 20% of oropharyngeal cancers are associated with HPV. In contrast to cervical cancers, genital warts have low malignant potential and are associated with low-risk HPVs, predominantly HPV-6 and HPV-11.

Epstein-Barr Virus.

EBV, a member of the herpes family, has been implicated in the pathogenesis of several human tumours: the African form of Burkitt lymphoma; B-cell lymphomas in immunosuppressed individuals (particularly in those with HIV infection or undergoing immunosuppressive therapy after organ transplantation); a subset of Hodgkin lymphoma; nasopharyngeal and some gastric carcinomas and rare forms of T cell lymphomas and natural killer (NK) cell lymphomas. Except for nasopharyngeal carcinoma, all others are B-cell tumours.

Hepatitis B and C Viruses.

Epidemiologic studies strongly suggest a close association between HBV infection and the occurrence of liver cancer. It is estimated that 70% to 85% of hepatocellular carcinomas worldwide are due to infection with HBV or HCV. HBV is endemic in countries of the Far East and Africa; correspondingly, these areas have the highest incidence of hepatocellular carcinoma.

Helicobacter pylori

First incriminated as a cause of peptic ulcers, *H. pylori* now has acquired the dubious distinction of being the first bacterium classified as a carcinogen. Indeed, *H. pylori* infection is implicated in the genesis of both gastric adenocarcinoma and gastric lymphomas.

The scenario for the development of gastric adenocarcinoma is similar to that of HBV- and HCV-induced liver cancer. It involves increased epithelial cell proliferation in a background of chronic inflammation.

3.5 Host Defense against Tumours—Tumour Immunity

The idea that tumours are not entirely self and may be recognized by the immune system was conceived by Paul Ehrlich, who proposed that immune recognition of autologous tumour cells may be capable of eliminating tumours. Subsequently, Lewis Thomas and Macfarlane Burnet formalized this concept by coining the term *immune surveillance*, which implies that a normal function of the immune system is to survey the body for emerging malignant cells and destroy them.

Tumour Antigens

Antigens that elicit an immune response have been demonstrated in many experimentally induced tumors and in some human cancers.[176] Initially, they were broadly classified into two categories based on their patterns of expression: *tumor-specific antigens*, which are present only on tumor cells and not on any normal cells, and *tumor-associated antigens*, which are present on tumor cells and also on some normal cells. This classification, however, is imperfect because many antigens thought to be tumor-specific turned out to be expressed by some normal cells as well. The modern classification of tumor antigens is based on their molecular structure and source.

1) *Products of mutated genes.* Neoplastic transformation, as we have discussed, results from genetic alterations in proto-oncogenes and tumor suppressor genes; these mutated proteins represent antigens that have never been seen by the immune system and thus can be recognized as non-self.
2) *Over-expressed or aberrantly expressed cellular proteins.* Tumor antigens may be normal cellular proteins that are abnormally expressed in tumor cells and elicit immune responses.
3) *Tumor antigens produced by oncogenic viruses.* The most potent of these antigens are proteins produced by latent DNA viruses; examples in humans include HPV and EBV.
4) *Oncofetal antigens.* These are proteins that are expressed at high levels on cancer cells and in normal developing (fetal) but not adult tissues. It is believed that the genes encoding these proteins are silenced during development and are depressed upon malignant transformation. Oncofetal antigens were identified with antibodies raised in other species, and their main importance is that they provide markers that aid in tumor diagnosis.
5) *Altered cell surface glycolipids and glycoproteins*. E.g. gangliosides, blood group antigens, and mucins.
6) *Cell type–specific differentiation antigens.* Tumours express molecules that are normally present on the cells of origin. These antigens are called *differentiation antigens* because they are specific for particular lineages or differentiation stages of various cell types. Such differentiation antigens are typically normal self-antigens, and therefore they do not induce immune response in tumour-bearing hosts. Their importance is as potential targets

for immunotherapy and for identifying the tissue of origin of tumours.

Antitumour Effector Mechanisms.

Cell-mediated immunity is the dominant anti-tumour mechanism in vivo. Although antibodies can be made against tumours, there is no evidence that they play a protective role under physiologic conditions.

1) *Cytotoxic T lymphocytes:* CD8+ CTLs play a protective role against virus-associated neoplasms (e.g., EBV- and HPV-induced tumors) and have been demonstrated in the blood and tumour infiltrates of cancer patients.
2) *Natural killer cells:* NK cells are lymphocytes that are capable of destroying tumour cells without prior sensitization and thus may provide the first line of defense against tumour cells. After activation with IL-2 and IL-15, NK cells can lyse a wide range of human tumours.
3) *Macrophages:* Activated macrophages exhibit cytotoxicity against tumour cells in vitro. T cells, NK cells, and macrophages may collaborate in antitumour reactivity, because interferon-γ, a cytokine secreted by T cells and NK cells, is a potent activator of macrophages.
4) *Antibodies:* Although there is no evidence for the protective effects of antitumor antibodies against spontaneous tumors, administration of monoclonal antibodies against tumor cells can be therapeutically effective. A monoclonal antibody against CD20, a B-cell surface antigen, is widely used for treatment of lymphomas.

Immune Surveillance and Escape

Most cancers occur in persons who do not suffer from any overt immunodeficiency. It is evident, then, that *tumor cells must develop mechanisms to escape or evade the immune system* in immunocompetent hosts. Several such mechanisms may be operative.

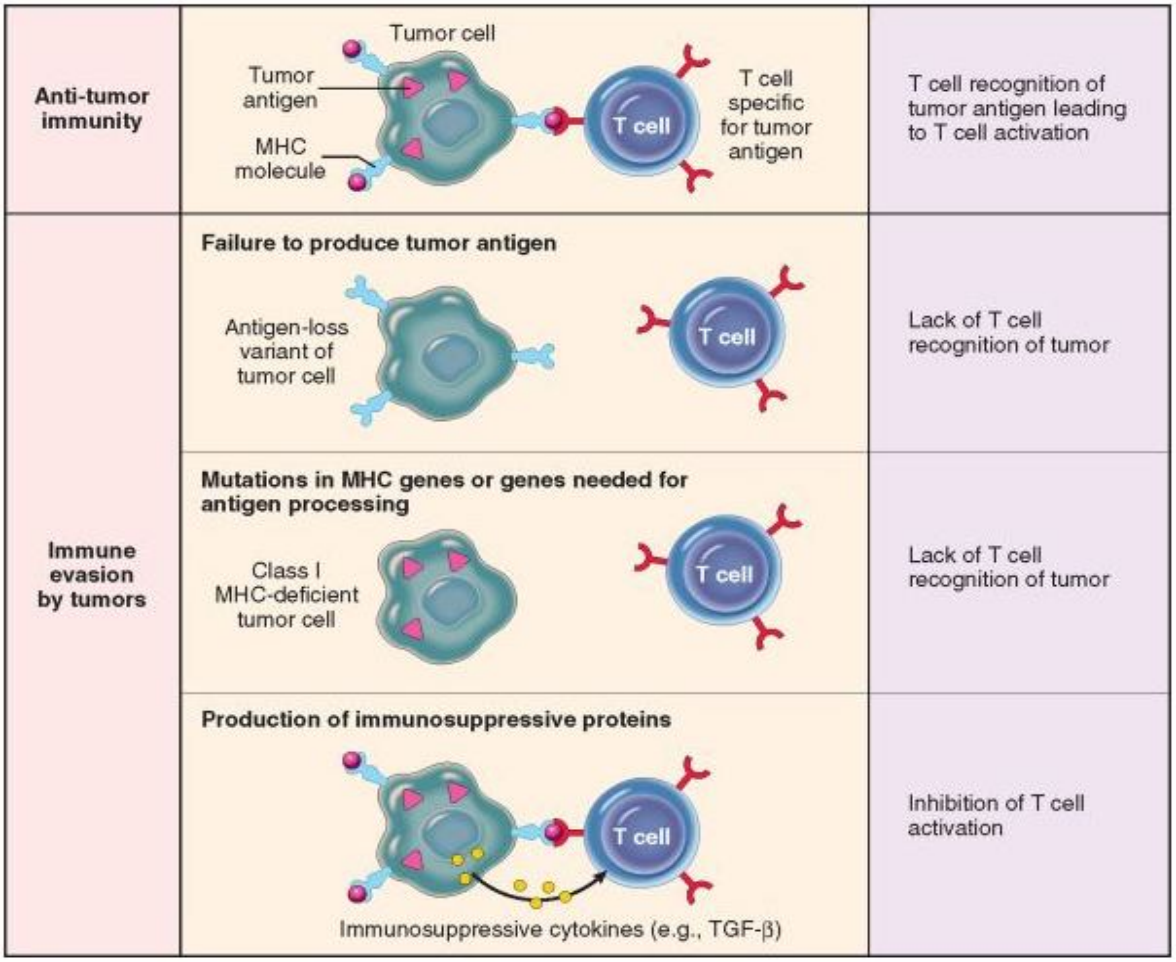

FIGURE 26. Mechanisms by which tumors evade the immune system. *(Reprinted from Abbas AK, Lichtman AH: Cellular and Molecular Immunology, 5th ed. Philadelphia, WB Saunders, 2003)*

It is worth mentioning that although much of the focus in the field of tumour immunity has been on the mechanisms by which the host immune system defends against tumours, there is some recent evidence that, paradoxically, the immune system may promote the growth of tumours.

It is possible that activated lymphocytes and macrophages produce growth factors for tumour cells, and regulatory T-cells and certain subtypes of macrophages may suppress the host response to tumours. However, harnessing the protective actions of the immune system and abolishing its ability to increase tumour growth are obviously important goals of immunologists and oncologists.

3.6 Clinical Aspects of Neoplasia.

Ultimately the importance of neoplasms lies in their effects on patients. Although malignant tumours are of course more threatening than benign tumours, any tumour, even a benign one, may cause morbidity and mortality. Indeed, both malignant and benign tumours may cause problems because of (1) location and impingement on adjacent structures, (2) functional activity such as hormone synthesis or the development of paraneoplastic syndromes, (3) bleeding and infections when the tumor ulcerates through adjacent surfaces, (4) symptoms that result from rupture or infarction, and (5) cachexia or wasting.

Local and Hormonal Effects

Location is crucial in both benign and malignant tumours. A small (1-cm) pituitary adenoma, though benign and possibly nonfunctional, can compress and destroy the surrounding normal gland and thus lead to serious hypopituatarism. Cancers arising within or metastatic to an endocrine gland may cause an endocrine insufficiency by destroying the gland. Neoplasms in the gut, both benign and malignant, may cause obstruction as they enlarge.

Cancer Cachexia

Individuals with cancer commonly suffer progressive loss of body fat and lean body mass accompanied by profound weakness, anorexia, and anemia, referred to as *cachexia*. Unlike starvation, the weight loss seen in cachexia results equally from loss of fat and lean muscle. There is some correlation between the tumor burden and the severity of the cachexia.

However, cachexia is not caused by the nutritional demands of the tumor. In persons with cancer, the basal metabolic rate is increased, despite reduced food intake. This is in contrast to the lower metabolic rate that occurs as an adaptational response in starvation. *Although patients with cancer are often anorexic, cachexia probably results from the action of soluble factors such as cytokines produced by the tumor and the host rather than reduced food intake.*

Paraneoplastic Syndromes

Symptom complexes in cancer-bearing individuals that cannot readily be explained, either by the local or distant spread of the tumor or by the elaboration of hormones indigenous to the tissue from which the tumor arose, are known as *paraneoplastic syndromes*. These occur in about 10% of persons with malignant disease. Despite their relative infrequency, paraneoplastic syndromes are important to recognize, for several reasons, some of which are:

1) They may represent the earliest manifestation of an occult neoplasm.
2) In affected patients they may represent significant clinical problems and may even be lethal.
3) They may mimic metastatic disease and therefore confound treatment.

4.0 CONCLUSION.

The pathogenesis of cancer, the mechanisms involved and the body response to cancer is still largely poorly understood. What is clear and worrisome is the fact that the burden on the individual and the society is unfathomably heavy.

The nurse clinician must be armed with some basic knowledge of this disease of so many theories, have astounding empathy on those who are in the process of ultimately 'giving in' to the scourge!

5.0 SUMMARY. This unit teaches us about:

1) The definition of neoplasia and its synonyms.
2) The differences between benign and malignant tumours.
3) The molecular basis of cancer.
4) The various classes of carcinogenic agents and their cellular interactions.
5) Host defense against tumours.
6) Clinical aspects of cancer and carcinogenesis.

6.0 TUTOR-MARKED ASSIGNMENTS:

- What do you understand by the term neoplasm?
- Differentiate between benign and malignant tumours.
- What are the principles involved in the molecular basis of cancer?
- Discuss briefly the following terms:
  - Oncogens.
  - Proto-oncogens
  - Tumour-suppressor genes.
- List 10 oncogens that you know, their modes of activation and disease entities where they are present.
- Write short notes on the followings:
  - Chemical carcinogenesis.
  - Radiation carcinogenesis.
  - Microbial carcinogenesis.
  - Tumour immunity.

8.0 REFERENCES /FURTHER READING.

- **Robbins and Cotran Pathologic Basis of Diseases. Eight edition**
- **Essentials of Pathology. By Emanuel Rubin. Third edition.**

MODULE 5.

UNIT 1: HANDLING OF BIOPSIES.

Objectives :

1) Exposure to specimens and slide preparation procedures.

2) Identification of pathological specimen and relation to relevant topics studied.

UNIT 2: POTS DEMONSTRATION.

Objective :

Identification of pathological specimen preserved in pots and relation to relevant topics studied.