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DEPARTMENT OF PATHOPHYSIOLOGY

Courses of pathophysiology

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FOREWARD

This manual focuses on alterations in biologic processes that affect the body's dynamic equilibrium or homeostasis, a conceptual approach designed to integrate knowledge from the basic and clinical sciences.
Pathophysiology deals with the dynamic aspects of disease processes. It is study of disordered or altered functions – the physiologic mechanisms altered by disease in the living organism. Pathophysiology provides the link between the scientific realm of anatomy, physiology, and biochemistry and its application to clinical practice. The study of pathophysiology is essential to understand the rationale for diagnosis and therapeutic intervention in disease conditions.

The book falls into two parts: the first, general pathophysiology, is devoted to basic mechanisms and the second, special pathophysiology, to the application of knowledge of these basic mechanisms to the understanding of pathogenesis of an exemplar condition. The general pathophysiology includes chapters on concepts of normalcy and disease, etiology of disease, evolution of disease, general pathogenesis of disease, adaptation and reaction of the body to the aggressive factors, cancerogenesis and disturbances of the metabolisms. The pathogenesis of respiratory, cardiovascular, digestiv, renal and blood disorders is disscused in the second part of the manual.

The overriding aim of this book is to meet the need for new approaches to learning medicine, beeing an interdisciplinary and integrative approach founded on deep understanding of normal and abnormal human biology.

I am grateful to my colleagues Veronica Mocanu, lecturer, Mariana Roşca, universitary assistant and Tiberiu Mustaţă, universitary assistant, for their valuable contributions. I thank Octavian Popârda, junior assistant, for assistance in preparation of the manuscript.

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I. GENERAL PATHOPHYSIOLOGY

I.1. CONCEPT OF NORMALCY AND DISEASE

A. Modern pathophysiology, is originated from experimental pathology, and became an integrative biomedical science. Pathophysiology studies:

1) Basic mechanisms of development of pathophysiological processes at different structural - and - functional levels of the organism.

2) Alterations in biologic processes that afect the **body's dynamic** equilibrium or homeostasis.

- Pathophysiolosy is a conceptual approach designed to integrate knowledge from basic and clinical science; deals with dynamic aspects of diseases processes.
- It is the study of disordered or altered **functions; the physiologic** mechanism altered by disease in the living organism
- Providies the basic link between the scientific realm of anatomy physiology and biochemistry and its application to clinical practice. It links fundamental disciplines (physiology, biochemistry, biophysics etc.) to clinical medicine, provides a way for the formation of biomedical mentality in physicians and is an indispensable part of medical education. Specialists of any profile, studying pathophysiological processes in various objects, are concerned with pathophysiological problems.

The study of pathophysiology is esential to understand the rationale for diagnosis and therapeutic intervention in disease conditions.

The hours of pathophysiology designed to meet the sophisticated needs of health care profesionals and it is essential to synthesize pathophysiologic concepts to understand the rationale for preventive measures and therapeutic interventions.

Pathophysiology - background for understanding the disease process.

The number and variety of human illnesses are imens, since every organ or system within the body is subject to disease. However, the basic ways in which an organ can become diseased are quite limited, and the large number of diseases represents different combinations and permutations of a smaller number of basic biologic processes that lead to the alterations of structure and functions.

Pathology is the science or study of disease. In its broadest sense, pathology is literally abnormal biology, the study of individual who are ill or d isordered.

Pathology in its simplest sens is the study of structural and functional abnormalities that are expressed as diseases of organs and systems.

As basic science, pathology includes as well as human pathology. In the context of human medicine, is not only a basic or theoretical science but also a clinical medical speciality.

Pathophysiology with the dynamic aspects of the disease process it is the study of disordered or alterated functions, for example, the physiologic changes caused by disease in a living organism.

Modern pathology is both a science and a clinical practice. As a science it focused on the mecanisms by which cells, tissues, and organs are injured and, on the structural changes that underline disease processes.

The clinical practice of pathology involves the use of molecular microbiological. immunologic and morphologic techniques on cells tissues, and fluids to establish the diagnosis and guide therapy diseases.

All forms of tissue injury start with molecular or structural alterations in cells. It is necessary then to begin our considerations of pathology, with one examination of disease at the cellular and subcellular levels.

The normal cell is a restless, pulsating microcosm, constantly modifying its structure and function in repause, to changing dema and stresses.

Until these stresses become too severe, the cell tends to mentain a relatively narrow range of structure and function, so called normal homeostazis.

There are two parts of Pathophysiology.

Fundamental disease, such as inflamation, neoplasia and general reactions of the body as answer at an agression will be described in the general part of Pathophysiology; the details of specific illnesses will be the object of study in the special part of Pathophysiology which will be studied in future.

B. GENERAL CONCEPT OF DISEASE PROCESSES

CONCEPT OF NORMALCY

Most people have some notion of normal and would define disease or ilness as a deviation from or an absence of that normal state. However, the concept of normalcy turns out to be complex and cannot be defined succintly; correspondingly, the concept of disease is far from simple.

Any parameter of measurement applied to an individual or group of individuals has some sort of average value that is considered normal. Average values for height, weight, and blood pressure are derived from observations on many individuals and include a certain amount of variation.

Variations in normal values occur for several reasons. First, individuals differ from one another in their genetic makeup. Thus, no two individuals in the world. except those derived from the same fertilized ovum, have exactly the same genes. Second, individuals differ in their life experiences and in their interaction with the environment. Third, in every individual there are variations in physiologic parameters because of the way in which the control mechanisms of the body function. For instance, blood glucose concentrations in a healthy person vary semnificantly at different times during the day, depending on food intake, activities of the individual, and so forth. These variations generally occur within a certain range. The situation is somewhat analogous to a thermiostatically controlled room. The temperature may dip slightly below the desired level before such a drop is sensed by the thermostat. The corrective action triggered by the thermostat may, in turn, overshoot the ideal slightly before the heat input is halted. Indeed, such variations in body temperature, even in the normal state, occur in all individuals. Finally, for physiologic parameters measured by fairly intricate means, a significant amount of variation in observed values may result from error or imprecision of the measurement process itself.

Because of these considerations determining a normal range of variation from an average value is a complex matter. This complexity includes knowing the degree of physiologic oscillation of a particular measurement, accounting for the degree of variation among normal individuals even under baseline conditions, and figuring the precision of the measurement method. Finally, the biologic significance of the measurement must be estimated.

Single measurements, observations, or laboratory results that seem to indicate abnormality must always be judged in the context of the entire individual. A single reading of elevated blood pressure does not make an individual hypertensive; a single slightly elevated blood glucose level does not mean tnat the individual is diabetic; and a single hemoglobin value lower than average does not necessarily indicate anemia.

To place the above considerations in perspective concepts of normalcy and even of disease are arbitrary and influenced by cultural values as well as by biologic realities. For example, in our culture a defect of a central nervous system function may produce a significant reading disability and would be an abnormality, whereas the same defect might never be noted in a primitive culture. Furthermore, a trait that might be average and thus normal in one population might be considered distinctly abnormal in another. Consider for instance how a "normal" person from our population would be viewed by a group of central African pygmies; or conversely, how an infant from a primitive culture, with the "normal" chronic diarrhea and poor weight gain, might be viewed in one of our well-baby clinics !

CONCEPT OF DISEASE

Disease can be defined as changes in indivudals that cause their health parameters to fall outside the range of normal. The most useful biologic yardstick for normalcy relates to the individual's ability to meet the demands placed on the body

and to adapt to these demands or changes in the external environment. All cells in the body need a certain amount of oxygen and nutrients for their continuing survival and function, and they also require an environment that provides narrow ranges of temperature, water content, acidity, and salt concentration. Thus, the maintenance of internal conditions within fairly narrow limits is an essential feature of the normal body. When some of the structures and functions of the body deviate from the normal to the point where the ability to maintain homeostasis is destroyed or threatened or where the individual can no longer meet environmental challenges, disease is said to exist. A person's subjective perception of disease is related to impairment of the ability to carry on daily activities comfortably.

Disease does not involve the development of a completely new form of life but rather is an extension or distortion of the normal life processes present in the individual. Even in the case of an obviously infectious disease, where the body is literally invaded, the infectious agent itself does not constitute the disease but only evokes the changes that ultimately are manifested as disease. Thus, disease is actually the sum of the physiologic processes that have been distorted. To understand and adequately treat the disease, the identity of the normal processes interfered with, the character of the disturbances, and the secondary effects of such disturbances on other vital processes must be taken into account.

Historically, it was believed that disease is actually a new form of life, a sort of possession of the body by an outside agent. From this notion it would follow that some form of exorcism to drive out the disease agent is proper therapy. However, even in the instance of an invasive infectious agent, attempted treatment with antibiotics alone, may not cure the patient if proper attention is not directed toward the intrinsic body processes that have become deranged.

A theme that will recur, with variations, is that disease above all is part and parcel of the patient. Normal and abnormal processes represent different points on the same continuous spectrum. In fact, the seeds of disease often lie within the adaptive mechanisms of the body itself, mechanisms that constitute a potential two-edged sword. For instance, the very same mechanism that allows us to become immune to certain infections evokes reactions such as high fever and asthma when some of us are challenged by particular environmental agents. Similarly, the mechanism of cellular proliferation that allows us to repair wounds and constantly renew cell populations in various tissues, may run amok, giving rise to cancer.

C. THE DEVELOPMENT OF DISEASE

Early in the development of a disease, the etiologic agent or agents may provoke a number of changes in biologic processes that can be detected by laboratory analysis even though there are no subjective symptoms. Thus, many diseases have a subclinical stage, during which the patient functions normally even though the disease

processes are well established. The structure and functions of many organs provide a large reserve or safety margin, and functional impairment may become evident only when the disease has become quite advanced. For example renal disease could completely destroy one, and partly destroy the other, before any symptoms related to decreased renal function would be perceived. However, some diseases seem to begin as functional derangements and actually become clinically evident although no anatomic abnormalities can be detected at the time. Such functional illnesses may lead to secondary structural abnormalities.

As certain biologic processes are encroached on, the patient begins to feel subjectively that something is wrong. These subjective feeling are called symptoms of disease. By definition, symptoms are subjective and can be reported only by the patient to an observer. However, when manifestations of the disease can be objectively identified by an observer. these are termed signs of the disease.

Nausea, malaise, and pain are symptoms, whereas reddening of the skin and a palpable mass are signs of disease.

I.2. GENERAL EVOLUTION OF DISEASE

A disease has no the same symptoms and signs for all patients. Every patient is "unique". The physician has to treat the patient, not the disease.

The evolution of the same disease is different to one patient to another or to the same patient depending to the nutrition, tiredness and age conditions. The various pathogenic agents determine different evolution of disease; however there are some comune characteristics stages for an acute disease:

I. Incubation period. This period lasts from seconds (strong poisons) until weeks (measle), months (hepatitis) and years (X-ray exposure, syphilis, leprosy). it begins once at the moment of agents action until the appearance of the symptoms of disease. This period is relatively asimptomatic and it can be named "preclinical changes period", but there are biochemical modifications

II. Invasion period, generally lasts a short times (1-3 days). it begins once at the initial symptoms, which can be specifically to the pathogen agent or nonspecifically (fever, adinamia, weakness, postration, headache, leucocytosis).

III. Clinical period, lasts from the appearance of all characteristics symptoms of the disease until the beginning of the decline. There is a great variability in the time of this period (8-10 days for measles, 4-6 weeks for hepatitis).

IV. Decline or convalescence period appears when the specific symptoms of disease decrease and lasts until the complete healing.

This pattern is especially for infectious diseases, but the majority of noninfectious disease have an stadial evolution too.

The evolution of chronic disease is also stadial, but the limit between the stages is unclear. The incubation and invasion last longer than in acute disease and clinical features are more or less diminuished depending to the efficiency of compensatory mechanisms.

The finishing or morbid process (disease). The disease can finish by healing, that means completely restablishing of the modified functions and total or partial disappearance of organic lesions. It is possible to finish it by a functional reshuffling, due to the involving compensatory mechanism. Other times the disease becames chronic or causes the death.

The healing can have two forms: total healing, which is call "restitutio ad integrum", with completely return to the normal structure and function and partial healing with persistence of some lesions or functional failure of injure organ.

One part of functional tissue can be replaced by sclerosis tissue which determine a certain degree of functional failure.

Sometimes, the compensatory process is so good that the failure is not manifested in conditions of reduced demands or in repose. Other times, even in repose conditions, the functional failure is manifested.

A complication of a disease is a new or separate process that may arise secondarily because of some change produced by the original entity. For example, bacterial pneumonia may be a complication of viral infection of the respiratory tract. Fortunately, many diseases can also undergo what is termed resolution and the host returns to a completely normal state, without sequelae or complications. Resolution can occur spontaneously, that is, owing to body defenses, or it can result from succesful therapy.

The death: it can appear after a chronic disease by gradually lose of the functions of whole organisms or by cease of cardiac and respiratory activities. like an acute accident in perfect health. It can distinguish two stages:

- clinical death (relative) in which major functions (circulation and breathing) are ceased. This period is very short, it lasts 5-8 min due to irreversibile nervous cells changed, in oxygen lack conditions.
- biological death (true) which appears once at the death of cells; the first to be affected are the nervous cells.

A demonstrable structural change produced in the course of a disease is referred to as lesion. Lesions may be evident at a gross and/or a microscopic level. The outcome of a disease is sometimes referred to as a sequel (plural sequelae). For example, the sequel to an inflamatory process in a given tissue might be a scar in that tissue. The sequel to acute rheumatic inflamation of the heart might be scarred deformed cardiac valves.

Finally, it is essential to reemphasize that disease is dynamic rather than Static. The manifestations of disease in a given patient may change from day to day as biologic equilibria shift and as compensatory mechanisms are brought into play. Environmental influences brought to bear on the patient will also affect the disease. Therefore every disease has a range of manifestations and a spectrum of expressions that may vary from patient to patient.

I.3. GENERAL ETIOLOGY OF DISEASE

Etiology, in its most general definitions, is the assignment of causes or reasons for phenomena. A description of the cause of a disease includes the identification of those factors that provoke the particular disease. Thus, *tubercle bacillus* is the etiologic agent of tuberculosis. Age, nutritional status and occupation are some other factors involved in the development of tuberculosis. The sufferance should be therefore considered the consequence of an etiologic complex.

Even in the case of an infectious disease such as tuberculosis the agent itself does not constitute th disease. Rather, all of the resulting responses to that agent, all the disturbances of biologic processes taken together, constitute the disease. Both a range of *extrinsic or exogenous factors* in the environment and a variety of *intrinsic or endogenous* characteristics of the individual concur in the etiology of a particular disease.

- **Extrinsic factors in disease.** Some important causes of human disease include infectious agents mechanical trauma, toxic, chemicals, rar ion, exposure to extreme temperatures, nutrition problems and psychological

stress. Although the above mentioned extrinsic factors are importar causes of human misery, a view of disease that only takes into account these factors is not complete Disease being actually part and parcel of the life of the affected individual, the intrinsic respond mechanisms of that individual and all of the biologic processes affected by a particular extrinsic agent should also be considered.

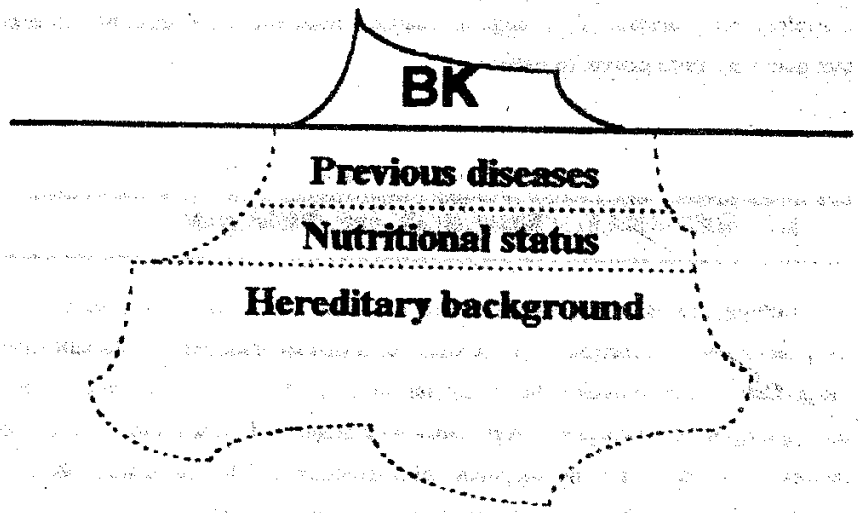


Figure no. 1 – Etiologic complex of tuberculous disease

➢ **Intrinsic factors in disease.** Many characteristics of the individual are intrinsic factor in disease, because they have a significant impact on the evolution of of various conditions. Age, sex and even abnormalities acquired during previous illnesses are factors to be considered in the pathogerlesis of a disease. Above all, genetic constitution or genome of the individual is an essential part of the "equation". This is because the anatomical characteristics

of the host, the physiological mechanisms of everyday life and the response modes against injury are all determined by the genetical information assembled at the moment of conception. In studying the biology of disease, heredity and environment should always be taken into account.

➢ **Induction of Estrinsic and Intrinsic Factors: a Spectrum.**

We often hear the question, "Is this disease hereditary?" In a sense, that question is improper. Since intrinsic factors are almost always involved in disease, be question should be phrased "To what extent is heredity important in this disease?". Exceptions to this principle are relatively few and quite extreme. Admittedly, heredity is not significant when the patient is involved in an explosion or struck by a speeding truck; but, such instances aside, it is always a factor. Even in a cleary exogenous infection genetic factors can and do influence susceptibility to the infectious agent and the pattern of disease produced.

There is a broad spectrum in the balance of heredity and environment in the causation of five groups of diseases. At the end of the spectrum are those diseases largely determined by some environmental agent irrespective the individual's hereditary background. At the other end are diseases that result from faulty gene programming. These diseases are expressed in almost any bearer of the faulty genetic informatic regardless of extrinsic influences and are commonly identified as hereditary diseases. Most human diseases lie between these two ends of the spectrum and involve a significant interplay between gene and extrinsic factors.

GE-NE-TIC FAC-TORS	DOMINANT GENETIC Cromosomial disease: - autosomal - gonosomal	PREPONDERENT GENETIC -G-6-PD deficiency	MIXT (50%) - Coronary disease - Diabetes Multi-factorial	PREPONDERENT ENVIRON-MENTAL Infectious diseases: - BK-Blacks	DOMINANT ENVIRON-MENTAL - Explosions - Strucks - Hemorrhage - Poisonning	ENVI-RON-MEN-TAL FAC-TORS

Figure no. 1'.

Representation of the ratio between genetical and ecological factors

The broad categories of causes of cell injure involve:

A. Extrinsic or exogenous factors in the environment:

- Chemical agents
- Physical agents
- Microbiological agents
- Nutritional imbalances

B. Intrinsic or endogenous factors characteristic to a particular individual:

- Genetic defects.

A. EXOGENOUS FACTORS

Chemical agents and drugs.

Virtually any chemical agent or drug may be involved in cell injuring by acting on some vital function of the cell such as:

a membrane permeability,

b. osmotic homeostasis or

c. the integrity of an enzyme or a cofactor.

Even an innocuous substance such as glucose, if sufficiently concentrated, may so derange the osmotic environment of the cell and thereby damage it.

A nearly endless list of chemical and biological agents injurious when inhaled, ingested, injected or absorbed through skin may be dressed. Therapeutic agents may provoke injuries while used for nearing an unrelated disease, non-therapeutic agents such as alcohol and a variety of other drugs of abuse may be accidentally or intentionally put in the body; they are used principally because of their psychotropic or mind-altering effects.

A number of important principles underly the understanding of the mechanisms of chemical injury.

• *Dose.* Generally, the higher the dose, the greater the toxicity, although small doses may cause serious sequelae, particularly over a protracted period

• *Requirement for metabolic conversion.* An alkali (certain cleaning materials) may be directly toxic to the cells. Conversely, many drugs including alcohol are converted within the liver to compounds more toxic than the parent substance.

• *Mode of action.* Many chemicals act directly on receptors or physiological receptor ligands and thus ordinarily affect only cells expressing the relevant receptor.

• *Sites of absorption, accumulation or excretion* For chemicals that are direct cell toxins, obviously the site is important in determining the type of injury. The site of accumulation is also important.

• *Individual variation.* The rates of absorption, metabolism and excretion all play a role in establishing the level of a chemical in plasma and thereby in tissues. Genetic polymorphism of drug metabolizing enzymes is another major determinant of the rate of drug metabolism.

• *Environmental agents or other drugs.* Environmental agents and other drugs may affect reactions to therapeutic agents. One of the most important pathways for drugs is the cytochrome P-450 enyzme (mono-oxidase) sytem in the liver. When this system is less active the drugs commonly inactivated by this system may accumulate and become more toxic.

• *The ability of the chemical to induce an immune response.* Several chemicals provoke injury by inducing an immune response. Factors that determine whether a substance initiates an immune response relate to both the chemical and the host.

Those related to the chemical include whether the compound is a protein large enough to act as an immunogen or, if very small, whether it can bind to a self protein and act as a hapter Host factors (i.e., immune response genes) are equally important.

INJURY BY THERAPEUTIC AGENTS

Adverse drug reactions refer to untoward effects of drugs given in conventional therapeutic settings. These reactions are extremely common in practice. Since estrogens and oral contraceptives (OC) are widely used we will overview these two classes of compounds.

a. Exogenous Estrogens and Oral Contraceptives.

Estrogens and OC-s will be discussed separately because (1) estrogens may be given alone in postmenopausal syndrome and (2) OC-s contain synthetic estrogens, always with progesterone.

Exogenous estrogens Estrogen therapy, once used primarily for the destressing symptoms of menopause, is now also used widely in postmenopausal women, with or without added progesterones, to prevent or delay progression of osteoporosis. Since estrogenous hyperestrinism enhances the risk of developing endometrial carcinoma and, likely, breast carcinoma, there is understable concern about the use of exogenous estrogens as therapeutic agents. Current data support the adverse effects of estrogen therapy

Cardiovascular disease. Myocardial infarction and stroke are among the leading causes of death in postmenopausal women. Estrogens elevate the level of high density lipoprotein (HDL) and reduce that of low-density lipoprotein (LDL). This lipide profile is protective against the development of atherosclerosis. Progesterone on the other hand tends to lower HDL and elevate LDL, which counters the estrogen effect.

Oral contraceptives. These drugs nearly always contain a synthetic estradiol and variable amounts of a progestin, but a few formulations contain only progestin. Currently prescribed oral contraceptives comain smaller amounts of estrogens and are clearly associated with fewer side effects than were earlier formulations. This shift began after 1975, and results of epidemiologic studies have to be interpreted in the context of the dosage. Nevertheless, there is reasonable evidence to support the following conclusions about the effects of these classes of drugs.

• *Breast carcinoma.* The breast cancer risk varies with estrogen content of the pill (both absolute and relative to the progestin content), duration of OC use, age at first use and interval between first use and time of the study.

• *Endometrial cancer.* No increased risk and very likely a protective effect.

• *Cervical cancer.* Some increased risk, correlated with duration of use.

• *Ovarian cancer.* OC-s protect against ovarian cancer.

• *Thromboembolism*. Using OC-s definitely increases venous thromboembolism risk.

• *Hypertension*. Even the newer OC-s formultions cause blood pressure elevations.

• *Cardiovascular disease*. As discussed, estrogens and progestins exert opposing effects on HDL and LDL levels. Recent evidence seems to absolve OC-s: it appears that non-smoking, healthy women under the age of 45 who use the newer formulations (low in estrogens) do not incur an increased risk of ischaemic heart disease.

• *Gallbladder disease*. The was a slight increase with older formulations, none with the newer ones. Obviously, the pros and cons of OC use must be viewed in the context of their wide applicabitility and acceptance as a form of contraception that protects against unwanted pregnancies with all their attendant hazards.

*b. **Acetaminophen***. When taken in very large doses (this widely used-the-counter) analgesic and antipyretic, causes hepatic necrosis. In some cases there is evidence of concurrent renal and myocardial damage. Acetaminophen toxicity is attributable to the formation of a toxic metabolite by the hepatic monoxidase system.

*c. **Aspirin***. Chronic aspirin toxicity (salicylism) may develop in persons who take 3 grams or more daily, a dose required to treat chronic inflammatory conditions. Chronic salicylism is manifested by headache, dizziness, ringing in the years (tinnitus), difficulty in hearing, mental confusion, drowsiness, nausea, vomiting, diarrhea, acute erosive gastritis, bleeding tendency and renal papillary necrosis.

Injury by non-therapeutic toxic agents

a. Lead. Acute lead poisonning may occur under unusual circumstances, e.g., battery burning. More commonly, lead compounds are accumulated slowly until they reach toxic levels Adults usually pretend with colicky abdominal pain, fatigue and pews headache, but in infants and children lead poisonning may remain unsuspected until it erupts in a cs trophic encephalopathic crisis.

In **children,** excess lead interferes with normal remodeling of calcified cartilage and primary bone trabeculae in the **epyphyses, leading to increased bone density** that is detected as radiodense lead "lines on radiographs".

Lead causes injury by binding, to disulfide groups in proteins including enzymes, altering their tertiary structure. The major anatomic targets of lead are the blood, nervous system, gastro-intestinal tract and kidneys

Blood changes resulting from lead accumulation. Lead interferes with normal heme biosynthesis by inhibiting the enzymes amino-levulinic acid dehydratase (ALA-

D) and ferroketolase (involved in incorporation of iron into the protoporphyrin molecule to form heme).

Blood changes are the following: elevated blood level of zinc-protoporphyrin or its product, free erythrocyte protoporphyrin (an important indicator of lead poisonning); microcytic, hypochromic mild hemolytic anaemia and punctate basophilic stippling of the erythrocytes.

Brain damage. In young children, sensory, motor, intellectual and psychologic impairments have been described, including reduced IQ, learning disabilities, retarded psychomotor development blindness. and in more severe cases, psychoses, seizures and coma. In adults, central nervous system is less affected, but frequently a peripheral demyelinating neuropathy appears, tipically involve the motor innervation of the most commonly used muscles.

Gastro-intestinal tract is also a major source of clinical features. Lead "colic" characterized by extremely severe, poorly localised abdominal pain, is often associated with sufficient spasm and rigidity of the abdominal wall to create the impression of an acute "surgical abdomen".

b. Carbon monoxide (CO). CO acts as a systemic asphyxiant. Hemoglobin displayes a 200-fold greater affinity for CO than for oxygen The resultant carboxyhemoglobin is unable of carrying oxigen and furthermore interferes with the release of oxygen from oxyhemoglobin. Systemic hypoxia occurs when the hemoglobin is 20% to 30% saturated with CO, and unconsciousness and death are likely with 60°/o to 70% saturation Depending on the rate of conversion to carboxyhemoglobin and the ultimate severity, one of two clinical patterns can be recognized.

Acute poisonnmg is marked by a characteristic generalized cherry-red color of the skin and mucous membranes resulting from carboxyhemoglobin.

• Chronic poisonning may appear because carboxyhemoglobin, once formed is remarkably stable and, with low-level persistent exposure, may accumulate to a life-threatening concentration in the blood. The slowly developping hypoxia may insidiously evoke widespread changes in the central nervous system.

c. **Alcohol and Other Drugs of Abuse.**

Pathology directly associated with alcohol abuse will be further discussed.

- **ETHANOL.** Eighty to ninety per cent of adults in many populations consume ethanol. Unfortunately, consumption is excessive in 5 to 10% of adult males and about 5% of adult females in most privileged societies.

The major effects of acute alcohol intake are exerted on CNS, but with chronic use other organs are also affected. Following ingestion, ethanol is absorbed unaltered

in the stomach and small intestine It is then distributed to all the tissues and fluids of the bodv in direct proportion to the blood level. Less than 10% of absorbed alcohol is excreted unchanged in the urine, sweat and breath. The amount exhaled is proportional to the blood level and forms the basis of the breath test employed by the law enforcement agencies.

Most of the alcohol in the blood is biotransformed to acetaldehyde in the liver through two pathways. Acetaldehyde formed by either pathway is further metabolised by acetaldehyde dehydrogenase. With relatively low levels of alcohol this conversion is mediated primarily by alcohol dehydrogenase. At higher levels the microsomal P-450 system becomes more important. Indeed, high blood levels of alcohol enhance the activity of this system, so that other drugs metabolised by the same pathway are more rapidly oxidized (some, unfortunately, to more toxic products). This partially explains the enhanced toxicity of certain drugs in alcoholics.

Acute alcoholism exerts its effects mainly on the central nervous system, but it may induce hepatic and gastric changes that are reversible in the absence of continued alcohol consumption.

Gastric changes constitute acute gastritis and ulceration. In the central nervous system, alcohol itself is a depressant, first affecting subcortical structures (probably the high brain stem reticular formation) that modulate cerebral cortical activity.

Consequently, there is stimulation and disordered cortical, motor and intellectual behavior

Chronic alcholism is responsible for morphologic alterations in virtually all organs and tissues in the body, particularly the liver and stomach.

Acetaldehyde, a major oxidative metabolite of ethanol is a very reactive compound and has been proposed as a mediator of the widespread tissue and organ damage. Although the catabolism of acetaldehyde is more rapid than that of alcohol, chronic ethanol consumption reduces the oxidative capacity of the liver, rasising the blood level of acetaldehyde, which is augmented by the increased rate of ethanol metabolism in the habituated drinker.

Whatever the basis, chronic alcoholics suffer significant morbidity and a shortened life spanrelated principally to damage to the liver, stomach, brain, heart and pancreas.

Liver. Alcohol, the most common cause of hepatic injury, may lead to cirrhosis.

Gastrointestinal tract. Massive bleeding from gastritis, gastric ulcer or esophageal varices (associated with cirrhosis) may prove fatal.

Central nervous system. A deficiency of thiamine is common in chronic alcoholics; the principal lesions of this deficiency are peripheral neurepathies and the Wernicke-Korsakoff's syndrome. Cerebral atrophy, cerebellar degeneration and optic neuropathy may also occur, possibly directly related to alcohol or its products.

Cardiovascular system. Direct injury to the myocardium may produce a dilated congestive cardiomyopathy. Although moderate amounts of alcohol have been shown to increase the levels of HDL and decrease the incidence of coronary heart disease, chronic alcoholism is associated with an increased incidence of hypertension.

- **COCAINE.** Both cocaine and its derivative Crack" have become major substances of abuse during the last decade; it is estimated that there are one to three million cocaine abusers in the United States. Cocaine is an aLkaloid extracted from the leaves of the coca plant that produces an intense euphoria with so called reinforcing qualities, malding it one of the most addicting of all drugs.

The most serious physical side effects of cocaine use relate to its acute toxic effects on the cardiovascular system and can be most readily understood by considering the sympathomimetic action of the drug. Cocaine acts to facilitate neurotransmission both in the central nervous system, where it blocks the reuptake of dopamine and at adrenergic nerve endings, where it blocks the reuptake of norepinephrine. The net effect is the accumulation of these two neurotransmitters at adrenergic nerve endings resulting in excess stimulation. Cocaine also exerts an additional, direct toxic effect on myocardium and peeps on skeletal muscle. These toxic effects are not necessarily dose-related and a lethal event may occur in a first-time abuser which if a typical mood-altering dose.

- **HEROIN.** Heroin is an addicting opioid (closely related to morphines derived from the poppy plant. It is short acting, so it must be taken evety few hours to avoid with drawal symptoms. Effects are varied and include euphoria, hallucinations, somnolence and sedation. Heroin has a wide range of adverse physical effects.

Sudden death, usually relaled to overdose.

Pulmonary complications include moderate to severe oedema, septic embolism, lung abscess, opportunistic infections and foreign body granulomas from talc and other adulterants.

Infectious complications are comrnon. The four siles most commonly affected are skin, subcutanesus tissue, heart valves, liver and lungs.

Cutaneous lesions are probably the most frequent telltale sign of heroin abdiction. Acute changes include abscesses, cellulitis and ulcerations due to subcutaneous injections.

Kidney disease is *a* relativelv common hazard. The two forms most frequently encountered are amyloidosis and focal glomerulosclerosis.

- **MARIJUANA.** Marijuana or pot is the most widely used illegal drug. It is made from the leaves of the Cannabis sativa plant, which contains the pyschoactive substance delta-9 tetrahydrocannabiol (THC).

The mortality and morbidity resulting from voluntary intake of tobacco smoke, alcohol, psychoactive drugs are more important than from all other environmental hazards combined.

Radiations, air pollution and industrial exposures are relatively minor dangers compared to the problems that people willingly bring upon themselves.

Physical agents

Physical agents have wide ranging effects on cells injuries. All physical agents have local and general effects and they may be divided into the following categories:

A. **Mechanical trauma.** Mechanical forces may inflict damage in several ways and the patterns of injury can be summarized in the following tenns:

- Abrasion = a wound produced by scraping or subbing.
- Laceration = a tear or disruptive stretching of tissue due to force application by a blunt object.
- Contusion = wound produced by a blunt object.
- Incised wound and Puncture wound

B. **Thermal injury.** Both excess heat (thermal bums or hypertermia) and excess cold (hypothermia) are important causes of injury.

Prolonged exposure to elevated ambient temperatures can result in systemic hyperteImia with heat cows, heat exhaustion and heat stroke (when high ambient temperature is associated with high umidity). In the meanwhile, localised hypertermia results in cutaneous burns while local focal thermal alterations range from inflammations to gangrene

Conversely, prolonged exposure to low ambient temperature leads to general hypothermia and beneath 32 °C loss of consciousness generally occurs, followed by bradycardia and atrial fibrillation at lower core temperatures. Coma may appear if temperature is less than 28° C. Subsequent decrease of respiratory rate, heart rate and blood pressure appear related to the decline of the functional reserves.

C. **Electrical injury** may arise from:

- low voltage currents (in the home or workplace)
- high voltage currents (high power lines)
- lightning

Two different types of injuries maw be described;

a.burns

b. ventricular fibrillation / cardiac and respiratory center standstill.

Both of them result from disruption of normal electrical impulses.The type of injury, the severity and the extent of burning depend on:

- amperage
- path of the electrical current within the body.

D. **Injury by ionizing radiation**

Radiation may simple be defined as the emission of energy by one body, its transmission through an intervening mediate and its absorption by another hady. Genetic cell damage is provoked either directly, by absorption of energy within the DNA or indirectly, by a reaction of the DNA. Injury by radiation - Ionizing radiation may directly damage DNA but more often it indirectly damages it by inducing the formation of free radicals, particularly those from the radiolysis of water. Ionizing radiation occurs in two forms:

1. electromagnetic waves (X - rays and gamma - rays);
2. high energy neutrons and charged particles (alpha, beta, protons).

The major effects of ionizing radiation are:

a. on DNA: - division inhibition
- aberant repair (teratogenesis / carcinogenesis).

b. on organ system

- Skin: - erythema, oedema (early)
- Lungs: - interstitial fibrosis (months to years)
- Gastro-intestinal tract: - mucosal injury (early)
  - ulceration (early)
  - wall fibrosis (late)
- Gonads: - germ cells distruction (early)
  - gonads atrophy and fibrosis (late)
- Blood and bone marrow: - thrombocytopenia
  - granulocytopenia
  - anaemia
  - lymphopenia

Adult brain is resistent to ionizing radiation. Radiant energy effect is accumulative delivery in divided doses may allow cells to repair some of the damages in the intervals.

E.**Sudden changes in atmospheric pressure**

Sudden changes in atmospheric pressure may cause two main syndromes:

1. acute altitude (mountain) sicknes (AAS)
2. decompression sickness (DS).

1. **Acute altitude (mountain) sickness** occurs in unnacclimatised individuals who ascend rapidly to height in excess of 2500 m. Most common symptoms are: headaches dyspneea, malaise, nausea, vomiting, abdominal pain and diarrhoea,

Modifications induced by high altitude are related to decreased atmospheric pressure and therefore to decreased oxygen availability. It has been suggested that the decreased oxygen tension and the limited ability of the lungs to extract it at lower pressures, produce hypoxia, that seems to be the most important factor in causing high altitude illness. The narrows reserve is illustrated by the finding that physical activity at this elevations leads to a decrease in the partial pressure of arterial oxygen whereas comparable physical activity at sea level does not change oxygen saturation. At sea level, cardiac output limits exercise whereas at high altitude the diffusing capacity of the luns for oxygen seems to be the determinant. Acclimation to chronic hypoxia at high altitudes results in a reduced ventilatory drive. Acclimated individuals have an increased number of capillaries per unit of brain, muscle and myocardium increases of myoglobulin within tissues; increased mitochondria per cell and an increased hematocrit. An increase in eryhtrocyte levels of 2',3-diphosphoglycerate, which enhances oxygen delivery tissues occurs within hours, but the induction of polycythaemia requires months. Some of the minor effects of high altitude are systemic oedema, retinal hemorrhages and flatus expulsion. The more serious non - fatal diseases are acute and chronic mountain sickness and high altitude deterioration. Fatal disease may develop in the form of high altitude encephalopathy.

- **High-Altitude Systemic Oedema.** High altitude systemic oedema results from an asymptomatic modification of vascular permeability, particularly in the hands, face and most often occurs at elevations over 3000 meters. It is reflected only in weight gain; upon return lo lower altitude, diuresis results in disappearance of oedema. This disorder is twice as common in women as in men. The cause of this peculiar condition is not known; an endothelial response to hypoxia provides only a partial explanation.
- **High-Altitude Retinal Hemorrhage.** A critical analysis by funduscopic examination revealed that 30% to 60% of those sleeping above 5000 meters had retinal hemorrhage. The initial effect includes retinal vascular engorgement and tortuous ness. Optic disc hyperemia is also noted and multiple flame-shaped hemorrhages subsequently occur. These changes are reversible.
- **High-Altitude Flatus.** Chances in external pressure and the production of intestinal gas provide for the expansion of the luminal contents of the intestine and increased flatus at altitudes above 3500 meters. No specific physical disease has been associated with these changes, although social problems have been encountered.

- **Acute Mountain Sickness.** Acute mountain sickness is rare below 2500 meters, but is present to some degree in nearly everyone at 3000 to 3600 meters The initial presentation includes headache, lassitude, anorexia, weakness and difficulty in sleeping. Pathophysiological mechanism underlying this disease are associated to hypoxia and a shift in the plasma fluid to the intestinal space. Adaptation through a modification of the pulmonary function (increased respiratory rate) causes some amelioration of the disease. Descent to lower altitudes is certainly indicated. Chronic or subacute exacerbation of this disease also occurs, frequently at lower altitudes, and symptoms may be severe. The basis of the disease is not known.
- **High-Altitude Deterioration.** High altitude deterioration, generally occuring at higher elevations (5500 meters or more) displays a decrease in physical and mental performance. The combination of chronic hypoxia, inadequate fluid intake and inadequate nutrition, together with decreased plasma volume and hemoconcentration are aggravating factors.
- **High-Altitude Pulmonary Oedema and Cerebral Oedema.** Serious high-altitude problems, including pulmonary oedema and cerebral oedema, may occur with a rapid ascent to heights over 2500 meters, particularly in susceptible individuals who poorly tolerate sleeping at higher altitudes. Tachycardia, right ventricular overload and a marked reduction of arterial oxygen pressure are commonly seen, while no change may be noted with respect to pH and carbon dioxyde retention. A characteristic patchy pulmonary infiltrate is seen radiographically. Pulmonary hypertension due to increased resistance is common in patients with high-altitude pulmonary oedema. Hypoxic vasoconstriction and intravascular thrombosis have been proposed as causes of pulmonary hypertension. Eventually, cardiac output is decreased and systemic blood pressure falls. Precapillary arterioles become dilated, increasing capillary bed pressure and inducing interstitial and alveolar oedema. Autopsy findings include severe confluent pulmonary oedema, proteinaceous alveolar exudates and hyaline membrane formation. Capillary obstruction by thrombi has been noted a dilated heart and enlarged pulmonssy arteries are commonly found. High-altitude encephalopathy is characterized by confusion, stupor and coma. Autopsies have consistently revealed cerebral oedema and vascular congestion. A proposed mechanism is severe cerebral hypoxia, with inhibition of the sodium pump and resultant intracellular oedema.

2. **Decompression sickness.** Deep diving and tunnell (caisson) work places a diver under an increased barometric pressure. If this is air, the nitrogen dissolved in blood (P_{N_2}) increases and, on rapid decompression, forms bubbles which come out of solution in small blood vessels. Ischemia results causing articular pain, spinal cord injury, chest pain, cyanosis, confusion, visual defects, paralysis and fits.

Microbiological agents

These agents range from submicroscopic viruses to large tapeform. In between are rickettsiae bacteria, fungi and higher forms of parasites. The ways by which biologic agents cause injury are:

- immune reaction
- inflammator reaction.

Nutritional imbalances

Imbalanced nutrition may provoke three major effects:

1. **Deficiences** in nutrition (marasmus). They are not only important causes of cellular injury but they could become serious public health problems in the future. Even today, unprivileged populations are suffering from protein - calorie severe deficiences.

2. **Avitaminoses** may be frequently submerged in concurrent protein energy malnutrition. They are increasing in deprived groups but may also be found in industrialized nations having relatively high standards of life.

3. **Excesses in nutrition** are significant causes of morbidity and mortality. Atherosclerosis obesity as well as vulnerability to a number of disorders occur in patients consuming diets rich in animal fats.

HYPOXIA commonly provokes cell injury and cell death by impinging on aerobic oxidative respiration. It may result from the following:

- loss of blood supply (ischemia) when arterial flow or venous drainage is
- inadequate oxygenation of the blood subsequent to respiratory failure
- loss of the oxygen-cariying capacity of the blood, e.g. in anaemia or carbon monoxyde poisonning (that produces a stable carbon monoxide hemoglobin blocking oxygen transport)

Conclusion: stresses that induce altered morphologic states in the cell range from gross physical violence to nutritional imbalances.

I.4. ADAPTATION AND DISEASE

INTRODUCTION

Adaptation is that process which allows the living organism to reach an optimal state-of-interaction with the environment. Even if it seems not complicated at the first glance, adaptation is such a complex process that one who tries to explain it from a single standpoint may find oneself at a high risk to miss an essential point. Moreover, adaptation as an achievement, seems to be correlated with two other processes: **development and learning.**

There is a psychological adaptation with its psychosexual and psychosocial aspects, and a biological adaptation. Since the psychological and the biological functions seem to be more correlated than expected, the subtle mechanisms which relates them are yet to be explored.

For a better understanding of the concepts we are going to talk about (i.e. adaptation and disease), an intuitive image of the mind/body system as a coherent dynamic network of agents and levels seems to be necessary. The attempt to recompose the image of the whole by collecting the data from different standpoints would disclose us the understanding strategies and the gaps to be filled.

- The organism is a multilevel hierarchic system that spans from molecules to the biological body and consciousness.
- Each level has its own program and specific characteristics which are more than the sum of the agents it is made of (e.g. a cell is more than the sum of molecules).
- The program of a level is subordinated to the program of the superior level. The autonomy of the levels is limited.
- The psychological processes, may they be conscious or unconscious, co-ordinate all the levels and direct the activity of the body as a whole towards specific goals.
- There are at least three systems which share the integration responsibility: nervous system, endocrine system, and immune system.

Briefly, adaptation is a process endowed with intentionality and which may be studied at different body level. There is systemic adaptation, may it be nervous, endocrine or immune, adaptation of a function, i.e. respiratory and cardiovascular, adaptation of an organ, of a tissue, a cellular and even a molecular adaptation.

From a psychological standpoint adaptation means a better fit in the environment, i.e. increased performance, defence, whereas the goal of physiologic

adaptations is maintenance of the organism's interior in a steady-state condition. When an organism can adjust its internal functioning to meet the requirements of the external environment, then the organism is in a state of ***homeostasis.***

Competence and performance

It is possible to make an analogy between the psycholinguistic concepts of competence and performance and the genotype/phenotype relation. Competence is the inborn capacity to learn a language: a generative grammar supported by neural mechanism whereas performance is the actual capacity of a native speaker to use his own language. In the same way the genome represents the capacity of the zygote to produce an individual whereas the performance is the phenotype as a result of interaction between the genotype and the environment.

- The performance system has its "weak spots" where less performant alleles are geared in their correspondent biomechanisms.
- Disease seems to be related to the weakness of these mechanisms when all the compensatory mechanisms are exceeded and the functional reserves are exhausted. The disease reveal a predisposition, but the logic of the process remains to be established.
- Ageing progressively loosens the performance system.

The concept of stress

In scientific terms the way the environment acts upon the individual is called stress.

The broadest definition of stress is a generalised, adaptive response, with marked physiologic and/or psychological changes, which is induced by environmental stimuli. Such stimuli, in turn, may be called stressors. There are **physical stressors** and **emotional stressors**.

It is necessary to reiterate that stress is essential for the organism in order to adapt and to react according to demand. In short, the stress response is fundamentally a coping mechanism. This kind of stress is called **benign** and sometimes it can be a lifesaving phenomenon since it is the very basis of the alarm, or "fight-or-flight" reaction. Some stress is an essential part of goal achievement, and frustration and troubles may even assist the development of character. Briefly, benign stress may be considered a mobilising agent that gears the body and the mind to a task that must be accomplished or a threat that must be avoided. However, the effects of the benign stress are beneficial only within certain constraints of severity and range of time. That is benign stress is benign as long as it does not harm the body and the mind. When the stress response goes beyond the gearing of the physiology and enters the realm of

pathophysiology the stress is called **malignant**. In any case, the response is basically malignant because it is either too severe or too prolonged or both. With physical insults, such as burns or prolonged body confinement, the stress reaction may be severe enough to cause secondary lesions in the gastric mucosa. This constitutes a state of distress.

Stressors as inducers of a systemic response

It is common usage in pathophysiology to employ the term "stressor" to indicate something that evokes a distress situation. In this sense, the range of things that can be or can become stressors is almost limitless. Today every form of illness - from whatever cause - is considered to be a stress factor.

Stress induction may be primarily emotional, as in the case of suppressed rage or anxiety, or it may be primarily physical, as in the case of burns and infections. In the former, perception is recognised as being a major factor in the ultimate severity of the stress. But in the latter, it is difficult to show how one's perception of a full thickness burn can ameliorate the actual condition of the tissues. Nevertheless, many clinical personnel emphasise the beneficial effects that the patient may gain by maintaining a "positive" attitude concerning his ultimate healing in any thickness. Clearly, many things transpire between the psyche and the soma that are not thoroughly understood at this time.

Physiologic mechanisms of the stress response

It was noted earlier that the stress response consists of a generalised network of physiologic reactions that are set into motion by some form of triggering agent. On the basis of extensive research, Hans Selye described a **"General Adaptation Syndrome"** which divides the body reaction into three successive stages:

1) alarm and mobilisation - a state of rapid, general arousal in which the body's defences are mobilised;

2) resistance - the state of optimal biological adaptation to stress;

3) exhaustion and disintegration - a stage reached when the body losses its ability to cope with prolonged stress

THE ALARM STAGE

Occurs shortly after the body "engages" the stressor. At this point the response is mediated largely by the cathecolamine hormones, norepinephrine and epinephrine, as a result of sympathetic activity. This is the stage of the stress response that most closely resembles a general alarm reaction because of the mobilising effect of the catecholamines. Adrenal steroid hormones, especially cortisol, are also secreted in

high quantities during this stage, and this increase is triggered by a rise in ACTH levels. Because of the release of these adrenal steroids and the catecholamines, the early phase of the alarm state often resembles a shock condition, and if the stressor is severe enough, death may occur at this time. But if there is an initial recovery, the alarm stage is characterised by a tendency toward general, bodywide mobilisation. This has been termed the countershock phase of the alarm stage because it resembles a reversal of the incipient shock condition.

THE RESISTANCE STAGE

Whereas the initial period of the alarm stage is dominated by epinephrine and norepinephrine, the resistance stages maintained by adrenal corticosteroids, most notably cortisol. In addition to the adrenal glands, other organs and tissues have been shown to undergo changes during the stage or resistance, including atrophy of the thymus, reduction of tissue volume of lymphatic organs, and decreased number of peripheral eosinophils.

The immune system become depressed, causing a suppression of

T cells. At least some of the effects of the resistance stage have been traced to the direct effects of high levels of cortisone, and so they are largely dependent on the duration of elevated serum cortisol.

If the system adapts and the stressor is removed, there is a return to a steady state.

If the system is unable to adapt or the stressor remains unchecked, the system moves to the final stage of GAS(General adaptation syndrome).

THE EXHAUSTION STAGE

If the stage of resistance is too prolonged, the many adaptive mechanisms of the body begin to show marked signs of failure. The stage of exhaustion may also be precipitated by a second stressor imposed during the resistance stage.

The immunologic defences of the body become depleted

As the name implies, physiologic collapse of one or more organs accompanies this failure.

The system enters into shock or death.

Mechanisms of GAS

NEURAL FACTORS

- **The hypothalamus** and the area adjacent to it is considered to be a pivotal component in the stress response. It receives neural input from the reticular formation of the brainstem, the limbic areas, and the thalamus. Psychological stress signals arrive at the hypothalamus via pathways from the high centers of the brain whereas

physiologic (somatic) stress approaches the hypothalamus from the lower centers of the brain.

- **The reticular formation** is another primary neural component of the response to stress. It is a major factor in maintaining consciousness and in "alerting" the higher centers once it has been stimulated by afferent input. The reticular formation is also affected by efferent impulses from higher centers and by the increased levels of epinephrine in the blood.
- The final neural pathway of the brain alert outflow is **the sympathetic division** of the autonomic nervous system. The neurohormone that activates the organs and thereby brings about the physiologic signs of stress is norepinephrine. The signs are amplified by the preganglionic fibers which synapse in the adrenal medulla to increase the secretion of epinephrine, which is blood borne.

The increased epinephrine levels appear to have a reciprocal effect on some brain areas, especially the reticular formation. Thus, the effect is self-reinforcing to some degree as long as the stimulus persists.

HORMONAL FACTORS

It is generally agreed that the stress hormones include the catecholamines (epinephrine and norepinephrine), some steroids including cortisol and aldosterone; ACTH and growth hormone.

Catecholamines have (1) cardiovascular, (2) metabolic, and (3) neural effects.

1. Catecholamine-mediated cardiovascular effects include:

increased arterial pressure due to tachycardia and vasoconstriction

selective shunting of blood to skeletal muscles

a tendency towards increased rates of blood coagulation

The overall outcome of the vascular changes is the gearing of the entire body for action (the basis of "fight-or-flight' reaction) by preparing the vascular bed for a more vigorous oxygen delivery to the needed tissues. Along with this, the adrenergic effect on the bronchioles is one of dilatation in order to increase oxygen delivery to the blood.

2 . Metabolic effects:

increased glycolisis in the muscles

a rise in the plasma glucose level

lipolysis and increased serum fatty acid levels

The effects serves to increase the general energy production

3. Neural effects

Epinephrine increases the neural activity of the ascendant reticular activation system which might explain the heightened mental alertness that is generally associated with the alarm reaction.

Cortisol effects:
elevation of blood glucose by gluconeogenesis
protein catabolism
depression of the immune system
ACTH increases secretion of glucocorticoids

Growth hormone promote protein synthesis and high elevations of the hormone probably block the destruction of proteins by cortisol induced gluconeogenesis In that case would exert a "protein-sparing" effect during a sustained stress response.

Antidiuretic hormone (ADH) secretion is probably increase by direct mediation of the hypothalamus nuclei to the neurohypophysis. The result of this hormone increase is conservation of fluid for the blood to compensate for fluid loss through sweating.

β-endorphin by its opiate properties appear to serve as a pain ameliorant during some stress conditions.

Bodywide adaptive mechanisms in the stress response

HEART ADAPTATION
- increased heart rate and contractility due to catecholamine effect
- increased cardiac output

BLOOD VESSEL ADAPTATION
- By means of **selective vasoconstriction and vasodilatation** skeletal muscle and neural tissue are furnished with an abundance of blood while nonessential organs such as the intestines undergo reduction in blood distribution.

RESPIRATORY ADAPTATION
- increased respiratory rate
- airways dilatation

KIDNEY ALTERATION
- renal vasoconstriction and decreased glomerular filtration rate
- increased ADH release
- decrease urinary output

SMOOTH AND SKELETAL MUSCLE ADAPTATIONS
- vasoconstriction/vasodilatation
- bronchodilatation
- increased muscular strength by epinephrine effect

ADRENAL GLAND ADAPTATION
- increased epinephrine and glucocorticoids release
- Histologic alterations

(1) hypertrophy during the time of cortisol production

(2) atrophy which eventually becomes apparent if the stress response enters the exhaustion stage

Pathophysiology of stress: a maladeptation

Factors that promote malignant stress:
- the innate severity of the stressor
- the length of time that the stressor persist
- the individual perception of the situation: the tissue damage often generates a more predictable response among different people than does psychological stress.
- The number of individual stressors that afflict the individual simultaneously: one stressor does not fortify the body against other, concomitant stressors.

General arousal in reaction to stress, however, does not explain why some people respond to such stress by developing ulcers, others migraine, and others high blood pressure. The question is not completely answers. In addition to general arousal, there are highly specific patterned responses that vary in accordance with the nature of both the stress and the individual.

Stimulus specificity - different kinds of stress produce different patterns of physiological response.

An experiment performed on the same subject showed that his flow of gastric juice decreased when he was exposed to stimuli that aroused his anxiety and increased when he was exposed to stimuli that aroused his anger. Fear and anger, it has been found, have significantly different effects not only on gastric activity but also on heart rate, blood pressure, muscle tension, respiration rate etc.. Changes in heart rate in response to stress may vary depending on whether requires that the person block out environmental stimuli, as in performing mental arithmetic problems, or attend closely to environmental stimuli, as in listening to a dramatic tape.

Individual response specificity - as a result of genes or of learning (probably both), people appear to have characteristic patterns of autonomic response which differ from one type of stress to another.

The first hint of this fact came in an experiment in which a group of people with histories of cardiovascular complaints (e.g. high blood pressure) and a group of people with histories of muscular complaints (e.g. backache) were both exposed to the same painful stimulus. Though the stressor was the same, the "cardiovascular" group responded with greater changes in heart rate than the 'muscular' group, while the 'muscular' group showed greater changes in muscular tension than the 'cardiovascular' group.

In other words, the subjects seemed to favour one or another physiological system in responding to stress.

Psychological stress and physical disorders

Abnormal psychology has been long recognized that medical disorders can be affected by emotional states. Recently, however, the relationship between psychological stress and physical illness has undergone a major reevaluation. Researchers used to believe that only certain disorders (asthma, ulcer, hypertension, migraine) were strongly influenced by psychological states. Now evidence suggests that almost any physical disorder, from cancer to common cold, can be to some extent "psychopathological".

This more holistic, or unified, concept of body and mind has led to the development of a new research discipline, **behavioral medicine** (also called *health psychology*). Three major historical trends have met in behavioral medicine:

- a trend toward holistic thinking: the recognition that our way of living and state of mind affect our physical well-being.
- the acknowledgement that science of psychology, with its accumulated wisdom regarding emotional and intellectual functioning has much to contribute to the study and cure of physical illness.
- The discovery that certain treatments pioneered by behavioral psychology, such as biofeedback and relaxation training, can help to relieve stress-related physical ailments.

PSYCHOLOGICAL EVENTS AND PHYSICAL ILLNESS: A DISREGULATION MODEL

Gary Schwartz has proposed a model for understanding stress-related physical disorders based on the concept of negative feedback.

***Negative feedback** is simply a specific kind of feedback in which the turning on of one component of a system leads to the turning off of another component, in order to regulate the system.*

As Schwartz points out, negative feedback loops are critical in the regulation of bodily processes. For example, in response to environmental stress, the nervous system may elevate the blood pressure. Blood pressure that rises too high, however, activates pressure sensitive cells called baroreceptors surrounding the blood vessels. The baroreceptors than send the message back to the nervous system, which in turn lowers the blood pressure.

According to Schwartz model it is when **this internal regulatory systems fail to operate properly** that diseases develop. Hence he calls his model a disregulation model. Disregulation can occur at any of four stages:

Stage 1: Environmental demands

The demands placed on the person by the environment is so high that one is forced to ignore negative feedback from the body so that one overwork the system.

Stage 2: Information processing in the central nervous system

Even if environmental demands are nor unreasonable, the brain may be programmed, either by genes or by learning, to respond inappropriately either to those demands or to the body's negative feedback.

Stage 3: Even if environmental demands are not excessive and the central nervous system (CNS) is processing information smoothly, the **peripheral organ** may be incapable of responding in an appropriate manner to the brain's instructions.

Stage 4: **Negative feedback**

Finally, even if environmental demands, CNS information processing, and the functioning of the peripheral organ are all normal, a problem may develop in the negative feedback loop

Essential hypertension

Stage 1: Environmental demands

It is possible that essential hypertensives are to some extent victims of the principle of stimulus specificity. That is, their condition may be due to the fact that their environments are particularly rich in the kinds of stressors that tens to increase blood pressure. Danger is one possibility.

Stage 2: CNS information processing

Essential hypertension may also be due in part to individual response specificity. In other words, genes or experience may have programmed the brain to respond to different kinds of stress with increases in blood pressure. In support of the genetic hypothesis, it is known that hypertension runs in families. Learning hypothesis tend to focus on how the person learns to handle feelings of aggression. It was long ago suggested that hypertensives are generally people who have difficulty venting anger. Recent research, however, has focused less on anger than on the simple matter of daily coping with controllable stress. In such research, some difficult but not impossible task is generally imposed on high risk subjects. One group assumed to be at risk for hypertension includes people with at least one hypertensive parent, and many studies have shown that such people, when confronted with demanding behavioral and cognitive tasks, do experience greater cardiovascular reactions than people without a family history of hypertension. The problem, then, may lie not with the stressor -after all, even the best lives contain a large measure of controllable stress - but with the individual. If so, these individuals need to design their lives and their responses to stress better than the rest of us.

Stage 3: The peripheral organ

Chronic hypertension produces structural changes in the blood vessels, so that they can no longer dilate properly. In other words, even if the brain is transmitting the right instructions the blood vessels are no longer capable of obeying them.

Stage 4: Negative feedback

Chronically high blood pressure may also, in time, affect the operation of the baroreceptors. Under the strain of chronically high pressure, the baroreceptors may eventually adapt to this stimulus and thus cease to respond to it properly.

It seems unlikely that any one of these forms of disregulation alone would be sufficient to produce chronic hypertension. In combination, however, they might tip the balance.

Cancer

A few decades ago researchers began to discover what seemed to be correlations between susceptibility to cancer and certain kinds of psychological characteristics like a marked tendency toward emotional restraint, the 'bottling up' of strong feelings, whether positive or negative. It seems that people able to express negative feelings - fear, horror, anger - about the disease were more likely to survive cancer than the more stoical types.

Besides emotional restraint, other psychological variables suspected as possible contributors to cancer are a sense of 'helplessness/hopelessness'. Animal studies seem to support the proposed relationship between the growth of cancer and the experience of helplessness in the face of stressful events.

In one study tumor cell were implanted in rats and then the rats were divided in three groups. One group received electric shocks that they could escape by pressing a bar. The second group received inescapable shocks, and the third group, no shocks. The experimenters found that the tumors grew more quickly in the rats given inescapable shocks than in either of the other groups.

- It is important to note that the proposition being tested in these experiments is not that stress causes cancer but that it influences the course of cancer, by draining the strength of the immune system.

This interaction between psychological factors and the immune system, mediated by the central nervous is now the focus of a rapidly developing subspecialty, **psychoneuroimmunology**. Psychoneuroimmunologists have established that stress does directly affect the immune system. They have also found that mental imagery can alter the workings of the immune system. In one study, highly hypnotizable subjects increased their immune response when, under hypnosis, they were given the suggestion that their white blood cells were 'powerful sharks' destroying 'weak germs'. Perhaps the best known psychological therapy for cancer patients is that developed by Carl and Stephanie Simonton, in which patients are encouraged to visualize defensive forces within their bodies attacking and devouring the cancer cells. The idea is to restore the patient's sense of control, a psychological change that presumably will lead to actual immunological control over the cancer.

THE BEHAVIORAL PERSPECTIVE

The conditioning of disregulation

There are two main points in this theory:

- the disorders may be explained as disregulation of autonomic nervous system conditioning
- the autonomic nervous system is under some kind of voluntary control

Imagine, for example, that a child tends to respond to an allergen such as dust with asthma attacks. If certain neutral stimuli were consistently paired with the experience of inhaling dust, then those stimuli could also become precipitating of attacks. Such explanation did not seem sufficient, however. First, if we assume that in many cases the conditioned stimuli were present without the unconditioned stimulus (the dust), then the conditioned response would have been difficult to acquire or would have been extinguished, unless it can be maintained by rewards. But this **operant conditioning** requires that the organism be capable of voluntarily modifying its response in order to obtain rewards or to avoid punishments. However, for years it was generally accepted that autonomic responses were involuntary, so that such conditioning was considered impossible. Then, in the sixties, a number of research reports suggested that autonomic responses such as the change in the heart rate, blood pressure, and urine formation could be modified by operant conditioning. One rat was even taught to dilate the blood vessels in one ear and at the same time to constrict the blood vessels in the other ear in response to a cue.

That discovery had two important consequences:

- First, it helped to explain how learning could operate in the development of physical disorders: if the disorder had any rewarding consequence, then these consequences might be maintaining the disorder through operant conditioning.
- Second, whether or not voluntary control was involved in the development of the disorder, it could be enlisted to relieve disorder.

Biofeedback training

Patients may be trained to recognize the autonomic responses of their bodies - to know what it feels like when their heart or blood pressure, for example, goes up and down. This type of training is known as biofeedback training. A hypertensive patient, for example, will be fitted with an apparatus that beeps as his blood pressure rises; a migraine patient will be hooked up to a machine that shows waves on a screen indicating the constriction and dilation of the blood vessels in her head. The patients, in other words, are given immediate feedback on their bodily functioning and then

somehow, through a process that we do not yet understand, they begin to exert control over this functioning.

It should be noted that biofeedback fits nicely into Schwartz's disregulation model. Many of the medical treatments for physical disorders serve to enhance disregulations. Drugs, for example, bypass the body's own regulatory capabilities and simply suppress the body's signals. Biofeedback, on the other hand, retrains patients to "listen" to their bodies and exercise their own capabilities to restore regulation.

Predictability and control

Two variables that seem to be particularly important in stress reactions are the predictability of stressful stimulus and the individual's control over the stimulus.

A research has shown that predictable stimuli are less stressful than unpredictable stimuli.

Moreover, control is apparently even more crucial.

As common sense would suggest, the subjective stressfulness of an experience depends less on how dangerous or painful it is than on how effective we expect to be in defending ourselves against the pain or danger.

These cognitive principles have been put into practice in so-called **stress management programs**. The goal of such programs is to pinpoint the cognitive and environmental sources of the patient's stress and then to build up skills he or she needs in order to cope with those stressors.

THE PSYCHODINAMIC PERSPECTIVE

Psychodinamic theorists regard most behavior as symptomatic of buried emotional content. Traditionally psychodynamic theorists have referred to stress-related physical disorders as organ neuroses.

Organ neuroses

Like anxiety, and dissociative disorders, such physical disorders as asthma, hypertension, and ulcer are regarded by psychodynamic theorists as related to disturbances in psychosexual development-disturbances that generate conflicts in the unconscious. As in the other neuroses, the conflict produces anxiety, and the anxiety is met with defence. In organ neuroses however, the defence leads to some somatic expression of the conflict (e.g. increased gastric secretion) which in turn leads to physical illness (e.g. ulcer).

Early psychodynamic theorists argued that the symptom was a convert expression of the conflict - that an ulcer, for example, was related to an oral conflict, colitis to an anal conflict, and so forth. But the current view is far less tidy. The psychodynamic theorists tens to see the organ neuroses as far less specific to the nature of the conflict.

Aside from recommending medical care when it is needed, psychodynamic therapists treat stress-related physical disorders no differently from any other anxiety-based disorder. The general goal is to identify the buried conflict, either -in orthodox psychoanalysis-by dream analysis and free association or-in modified psychodynamic theories -by face-to-face discussion of problems and their roots in the past.

Personality theories

Several decades ago psychodynamic theorists attempted to link "symptom choice" not only to the nature of the conflict but also to personality type. The thesis of the book *Type A Behavior and Your Heart* by Friedman and Roseman is that hypertension, along with other cardiovascular disorders tends to strike a specific kind of personality, which they call type A. Type A people are aggressive achievers. They talk, walk, and eat rapidly, and are highly impatient. They fidget in frustration if kept waiting by an elevator or a traffic light. They finish other people's sentences for them, they pride themselves on getting things done in less time than other people, and they measure their own performance by rigorous standards. In short they keep themselves under unremitting pressure - pressure that eventually takes its toll on their cardiovascular systems. *It seems that the cardiovascular systems of type A people may be overresponsive to competitive stress.*

Type A and type B (the more relaxed, patient executive) college students were asked to play computer Ping-Pong. At a certain point experimenters began to drop derogatory remarks about the subject's performance. These criticism led to increases in blood pressure, heart rate, and adrenaline secretion in the type A's but not in the type B's. This persuasive evidence has led to a series of programs designed to teach type A's to cope with stress in more type B fashion, and thus prevent heart disease. After three years of experiment the recurrence of heart attacks in the patient who had already suffered a heart attack was significantly lower in the type A counselling group comparing to control. This finding suggests that heart disease is related to type A behavior and that type A's can control heart disease by altering their behavior.

The sociocultural perspective

Several theorists claim that a major source of disregulation is to be found at stage 1, in the pressures that society places on the individual. In his volume *Man's presumptuous brain*, Albert Simeons argues that many physical disorders stem from a basic conflict between the social mores and biological instincts. According to Simeons the "fight-or-flight" response the state of intense sympathetic arousal which prepares the body in the face of danger is maladaptive for the human beings due to the cultural evolution. While other animals can still fight or flee, human beings are taught to "reason" with their enemies, resist quietly, "stay cool", or try some other

civilized strategy. Unfortunately, these indirect solutions, even if they take care of the threat, are much less efficient than direct physical action in returning the body to a state of balance. The arousal remains bottled up inside the body and fosters physical disorders.

The neuroscience perspective

Such disorders as ulcer, asthma, and hypertension are probably due not to stress alone but to stress operating on bodies that are predisposed to these disorders.

- **Genetic predisposition** see the genetic predispositions (certain disorders associated to certain HLA alleles) correlated to certain patterns of immune response performance
- **Somatic weakness** a psychophysiological complaint is most likely to develop in a person's most vulnerable organ system

Cellular adaptation & cellular injury

I. CELLULAR ADAPTATION

I.1 GENERAL CONCEPTS

The physiologic adaptation represents responses of the cells to normal changes in their dynamic molecular environment: the pattern of action of growth factors, hormones, nutrients etc.

Pathologic adaptation may share the same underlying mechanisms, but they provide the cells with the ability to survive in their environment and perhaps escape injury.

There are numerous types of cellular adaptations. For instance:

- down- or up-regulation of specific cellular receptors involved in the metabolism of certain components
- induction of new protein synthesis by the target cell, as in the heat shock response.
- producing one type of a family of proteins instead of another or markedly overproducing of one protein

These adaptations involve all steps of cellular metabolism of proteins - *receptor binding, signal transduction, transcription, translation, or regulation of protein packaging and release.*

STRESS (HEAT-SHOCK) PROTEINS AND CELL INJURY

One of the most highly conserved responses in biology is the induction of stress proteins by potentially injurious stimuli. Initially called heat-shock proteins (HSP) because they were described in the fruit fly larvae after slight elevation of

temperature, these molecules appear to be essential to cell survival in all species subjected to injury. In mammalian cells, they are induced by a variety of physical and chemical agents and by ischemia.

Heat-shock proteins are present constitutively in normal cells, where they play an important role in normal cell metabolism. Two families of such proteins called Hsp70 and Hsp60 (also called **chaperones**, or **chaperonins**) are intimately involved in intracellular protein folding and translocation as well as targeting of proteins to their final destination. Another, **ubiquitin**, is a small heat-shock protein that is critical to protein degradation because intracellular proteins destined to be degraded are first covalently modified by conjugation. Thus in stress, it is thought that the chaperonins "rescue" unfolded or aggregated polypeptides, and ubiquitin facilitates the degradation of protein denaturated beyond repair, thus protecting the cell from further injuries. Heat shock proteins have been shown to be induced in myocardial and neuronal ischemic injury. The capacity of certain areas in the nervous system to survive an ischemic attack is correlated with the increased expression of stress proteins.

TYPES OF CELLULAR ADAPTATION

1. Hyperplasia constitutes an increase in the number of cells in an organ or tissue, which may then have increased volume. Hyperplasia can be physiologic or pathologic.

Physiologic hyperplasia can be divided into:

- **hormonal hyperplasia** - e.g. the proliferation of the glandular epithelium of the female breast at puberty and during pregnancy
- **compensatory hyperplasia** - e.g. the hyperplasia that occurs when a portion of the liver is removed.

Mechanism of compensatory hyperplasia (fig. 2):

- priming of the hepatocytes - preliminary stimuli act on the cells and prepare them for the action of the mitogens
- action of the growth factors: TGF-α, hepatocyte growth factor (HGF)
- activation of the proto-oncogenes involved in cell proliferation
- activation of the growth inhibitors (TGF-β) and cessation of growth when the liver mass have been restored

Pathologic hyperplasia

Most forms of hyperplasia are instances of excessive hormonal stimulation or are the effects of growth factors on target cells. An example of hormonally induced hyperplasia is hyperplasia of the endometrum. After a normal menstrual period, there is a rapid burst of proliferative activity potentiated by pituitary hormones and ovarian estrogen which is brought to a halt by the rising level of progesterone about 10 to 14 days before the anticipated menstrual period. If the balance between estrogen and progesterone is disturbed with absolute or relative increase in the amount of estrogen

there will be hyperplasia of the endometrial glands. If the estrogenic stimulation abates, the hyperplasia dissapears. Thus, it responds to regular control of cells. It is this response to normal regulatory control mechanisms that differentiate benign pathologic hyperplasia from cancer. However, it should be stressed that *pathologic hyperplasia constitutes a fertile soil in which cancerous proliferation may arise.*

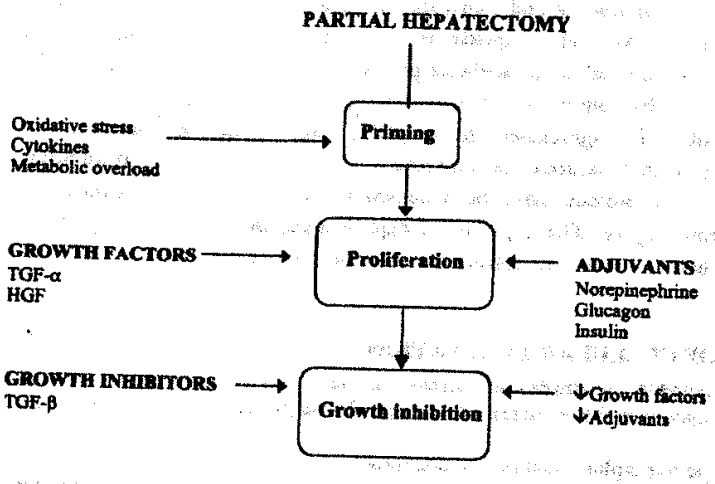


Figure no. 2
Mechanism of liver compensatory hyperplasia

2. Hypertrophy refers to an increase in the size of cells and, with such change, an increase in the size of the organ. Hypertrophy can be physiologic or pathologic.

In the heart, the most common stimulus for hypertrophy is chronic hemodynamic overload, due either to hypertension or to faulty valves. Synthesis of more proteins and filaments occurs, achieving a balance between the demand and the cells functional capacity. The greater number of myofilaments permits an increased workload with a level of metabolic activity per unit of volume of cell not different than that borne by normal cell. Not only the size but also the phenotype of the individual myocytes is altered in hypertrophy. In volume overload, for example, there is a switch of proteins to fetal or neonatal forms. Myosin and actin contractile isoforms change resulting in slower velocity of contraction in the hypertrophied fibers.

The triggers for hypertrophy and for these changes in gene expression consist on at least two groups of signals: **mechanical triggers**, such as stretch, and **trophye**

triggers, such as polypeptide growth factors and vasoactive agents (angiotensin II, alpha-adrenergic agonists).

Whatever the exact mechanism for hypertrophy would be, it eventually reach a limit beyond which enlargement of muscle mass is no longer able to compensate for the increased burden, and cardiac failure ensues. At this stage, a number of degenerative changes occur in myocardial fibers, of which the most important are lysis and loss of myofibrillar contractile elements. The limiting factors for continued hypertrophy and the causes of cardiac dysfunction are poorly understood; they may be due to the limitation of the vascular supply to the enlarged fibers, diminished oxydative capacities of the mitochondria, alterations in protein synthesis and degradation, and cytoskeletal alterations.

3. Atrophy is the shrinkage in size of the cell by loss of cell substance.
The causes of atrophy are the following:

- decreased workload
- loss of inervation
- diminished blood supply
- inadequate nutrition
- loss of endocrine stimulation
- aging

Atrophy represents a reduction in the structural components of the cell. The cell contains fewer mitochondria and myofilaments (muscle cell) and a lesser amount of endoplasmic reticulum. The biochemical mechanisms responsible for the atrophy are incompletely understood but it must be stressed that there is a finely regulated balance between protein synthesis and degradation in normal cells, and either decreased synthesis or increased catabolism, or both, may cause atrophy. Hormones, particularly insulin, thyroid hormones, glucocorticoids, and prostaglandines influence such protein turn-over.

In late adult life, the brain undergoes progressive atrophy, presumably as atherosclerosis narrows its blood supply, and the sex glands shrink with the depletion of endocrine stimulation. Some of these stimuli are physiologic (e.g. the loss of endocrine stimulation following the menopause), whereas others are clearly pathologic (e.g. loss of nerves).

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

The most common adaptive metaplasia is columnary to squamous, as occurs in the respiratory tract in response to chronic irritation as smoking. Even if the more

rugged stratified squamous epithelium is able to survive under circumstances in which the more fragile specialized would have succumbed, the influences that predispose to such metaplasia, if persistent, may induce cancer transformation in metaplastic epithelium.

Metaplasia is thought to arise from genetic reprogramming of stem cells that are known to exist in most epithelia, or of undifferentiated mesenchymal cells present in the connective tissue. Chemicals, vitamins, or growth factors most likely play a role in such metaplasias.

II.CELLULAR INJURY & CELLULAR DEATH

Cell death is the ultimate result of cell injury but it is also a normal process in embriogenesis, lymphoid tissue development, and hormonally induced involution. Moreover, it represents the aim of cancer radiotherapy and chemotherapy.

II.1. Causes of cell injury:

- hypoxia
- physical agents
- chemical agents and drugs
- infectious agents
- immunologic reactions
- genetic derangements
- nutritional imbalances

II.2. Vulnerable cellular mechanisms

Although it is not always possible to determine the precise biochemical site of action of injurious agent, four intracellular mechanisms are particularly vulnerable:

- maintenance of integrity of cell membranes, on which the ionic and osmotic homeostasis of cell and its organelles depends;
- aerobic respiration involving oxidative phosphorilation and production of adenosine triphosphate (ATP)
- synthesis of enzymatic and structural proteins
- preservation of the integrity of the genetic apparatus of the cell

II.3.General principles of cell injury

- The structural and biochemical elements of the cell are so closely inter-related that whatever the precise point of initial attack, injury at one locus leads to wide-ranging secondary effects. For example, impairment of aerobic respiration disrupts the energy-dependent membrane sodium pump that maintains the ionic and fluid balance of the cell resulting in alterations in the intracellular content of ions and water.
- The morphologic changes of cell injury become apparent only after some critical biochemical system within the cell has been deranged.
- Reactions of the cells to injurious stimuli depend on the type of injury, its duration and its severity.
- The type, state, and adaptability of the injured cell also determine the consequence of cell injury.

II.4. Main biochemical themes in cell injury & cell death

There are four common biochemical themes that appear to be important in the mediation of cell injury and cell death, whatever the inciting agent. These include the following:

1. Oxygen derived free radicals

One important mechanism of membrane damage is injury induced by free radicals, particularly by activated oxygen species. Free radicals are extremely reactive chemical species which are unstable and enter into reactions with proteins, lipids, carbohydrates - particularly with key molecules in membranes and nucleic acids. Moreover, free radicals initiate autocatalytic reactions whereby molecules with which they react are themselves converted into free radicals to propagate the chain of damage. Particularly relevant reactions are lipid peroxidation, oxidative modification of proteins and lesions in deoxyribonucleis acid (DNA).

It is a final common pathway of cell injury in such varied processes as reperfusion, chemical and radiation injury, cellular aging, microbial killing by phagocytic cells, inflammatory damage, tumor destruction by macrophages etc.

2. Loss of calcium homeostasis

Ischemia and certain toxins cause an early increase in cytosolic calcium concentration, owing to the net influx of calcium across the plasma membrane and the release of calcium from mitochondria and endoplasmic reticulum. Increased Ca^{2+} in turn activates a number of enzymes, with potential deleterious effects. The enzymes known to be activated by calcium include **phospholipases** (thus promoting membrane damage), **proteases** (which break down both membrane and cytoskeletal proteins), **ATPases** (thereby hastening ATP depletion) and **endonucleases** which are associated with chromatin fragmentation).

3. ATP depletion

Decreased ATP synthesis and consequent ATP depletion are common consequences of both ischemic and toxic injury. ATP is required for many synthetic and degradative processes within the cell. These include membrane transport, protein

synthesis, lipogenesis. There is ample evidence that ATP depletion plays a role in the loss of the integrity of the plasma membrane that characterizes cell death.

4. Defects in membrane permeability

Early loss of selective membrane permeability leading ultimately to overt membrane damage may be the result of a series of events involving ATP depletion, and calcium modulated activation of phospholipases. The plasma membrane, however, can also be damaged directly by certain bacterial toxins, viral proteins, lytic complement components, products of cytolytic lymphocytes (perforins), and a number of physical and chemical agents.

III. Patterns of cell death

There are two morphologic patterns of cell death, **NECROSIS** and **APOPTOSIS.** Despite the important differences concerning both the mechanism and the triggering context, there is also overlap between these two processes. They are morphologic patterns of acute cell injury induced by various stimuli.

III.1. Necrosis

Necrosis refers to a spectrum of morphologic changes that follow cell death in living tissue, largely resulting from the progressive degradative action of enzymes on lethally injured cells.

Due to its large impact on public health, especially related to cardiovascular diseases, acute ischemic necrosis (fig. 3) has been extensively studied in both experimental animals and culture systems. The cascade of events which follows the interruption of oxygen supply is poorly regulated in ischemic necrosis. Cells cannot adapt to a severe agression such as long standing oxygen deprivation because the internal mechanisms which keeps the steady state are overwhelmed. Thus, the cells are destroyed. During necrosis cells are mere witnesses of their death. Things are different in apoptosis where the cells are actively involved in their death. Furthermore, necrosis interests many cells at once, whereas in apoptosis single cells are selected for death.

In both cases cellular changes are reversible at the beginning. The outcome depends on the kind, severity and duration of thanatogenic (death inducing) stimuli.

REVERSIBLE INJURY

Biochemical changes

- decrease of oxidative phosphorilation and subsequent diminished ATP production
- depresion of ATP-dependent cellular processes (e.g. impaired heart muscle contraction)

- stimulation of anaerobic glycolysis and glycogenolisis.
- accumulation of lactic acid and subsequent acidosis
- loss of electrolyte homeostasis and cell volume regulation caused by the impared activity of ATP-ases (Na^+ - K^+ ATP-ase).

Cytological changes

- Acute cellular edema occurs as a result of intracellular osmotic load: accumulation of Na^+ and catabolites (inorganic phosphates, lactate, purine nucleosides).
- dilation of endoplasmic reticulum
- detachment of ribosomes from the granular endoplasmic reticulum
- dissociation of polysomes into monosomes (probably owing to disruption of the energy-dependent interactions between the membranes of the endoplasmic reticulum and its ribosomes).
- blebs may form at the cell surface and cells that posses microvilli begin to lose their normal microvillous structure

Up to a certain point, all of these disturbances are reversible if oxygenation is restored.

IRREVERSIBLE INJURY

In spite of the fact that there is no universally accepted biochemical explanations for the transition from reversible injury to cell death, two phenomena consistently characterize irreversibility.

- inability to reverse mitochondrial dysfunction and subsquent severe ATP depletion
- development of profound disturbances in membrane function

Several biochemical mechanisms may contribute to the membrane damage:

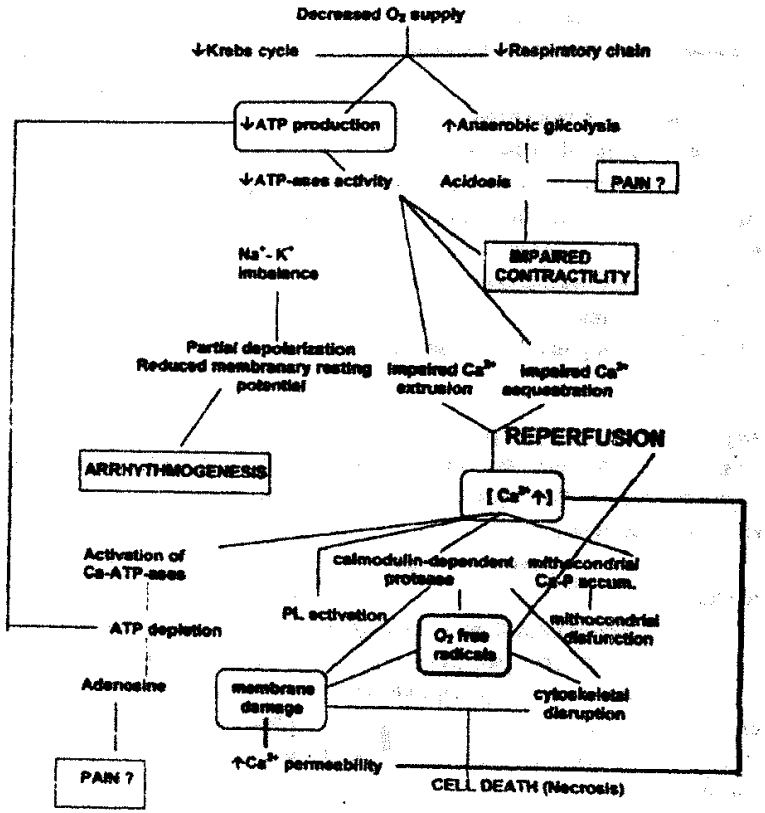
1. **Progressive loss of phospholipids** as a result of calcium dependent phospholipases activation (PLA_2) coupled with decreased reacylation or de novo synthesis of phospholipids. These latter reactions require ATP and appropriate substrate availability.

2. **Cytoskeletal abnormalities**. It is known that cytoskeleton connects the plasma membrane to the cell interior. Threfore, calcium induced protease activation, which cause damage to the cytoskeleton, renders the membrane susceptible to stretching and rupture.

3. **Reactive oxygen species** are highly toxic for membranes and other cell constituents. Their effect includes lipid peroxidation of membranes, oxidative modifications of proteins, and lesions in deoxyribonucleic acid. Such free radicals are present at very low levels in myocardium during ischemia, but there is an increase in

free radical production on restoration of blood flow. Reperfusion results in a paradoxic effect: an increase in damage called reperfusion injury.

STEPS OF NECROTIC CELL DEATH IN MYOCARDIAL ISCHEMIA AND REPERFUSION



4. **Lipid breakdown products** (unesterified free fatty acids, acyl carnitine, and lysophospholipids) have detergent effects on membranes. They also insert into the lipid bilayer of the membrane or exchange with membrane phospholipids, potentially causing changes in permeability and electrophysiologic alterations.

Whatever the mechanisms of membrane injury, the resultant loss of membrane integrity causes further influx of calcium from the extracellular space. When, in

addition, the ischemic tissue is reperfused to some extent, as may occur in vivo, the scene is set for massive influx of calcium. Calcium is taken up avidly by mitochondria after reoxygenation and permanently poisons them, inhibits cellular enzymes, denaturates proteins, and cause the cytologic alterations characteristic of coagulative necrosis.

Cytological (morphological) changes

- mitochondrial changes: severe vacuolization of mitochondria, development of amorphous densities in the mitochondrial matrix
- swelling of lysosomes, injury of lysosomal membranes followed by leakage of enzymes into cytoplasm and activation of acid hydrolases.
- Nuclear changes appear in the form of three patterns:
  - karyolysis - fading of the chromatin basophilia that presumably reflects DNAase activity
  - pyknosis - nuclear shrinkage and increased basophilia
  - karyorhexis - fragmentation of pycnotic nucleus

III.2. APOPTOSIS

Apoptosis is a morphological pattern that reflects a genetically-mediated pathway of cell death. The following morphologic features best seen with the electron microscope, characterize cells undergoing apoptosis:

- cell shrinkage
- chromatin condensation
- formation of cytoplasmic blebs and apoptotic bodies
- phagocytosis of apoptotic cells or bodies

This means that each cell is endowed with a specific genetic death program which accomplish cell disolution when triggered by various stimuli. Therefore, apoptosis is a more regulated event than necrosis, having the cells actively involved in their own death. The cell is not merely killed, it rather suicides.

The morphological term of apoptosis is sometimes understood as programmed cell death (PCD). But this is a common misunderstanding. Clasically, PCD is known to occur in embriogenesis, when normal but unwanted cells are removed. In this case the cells bear an internal device which beeps when the cells' lifetime has been exhausted, activating the program of self destruction. Here, the decision of suicide is entirely endogenous. There are many other situations when the cellular death program is activated by external stimuli. Here, the cell is pushed to die. The death order is then neatly performed by a dedicated internal program. In both cases apoptosis is the pattern of death.

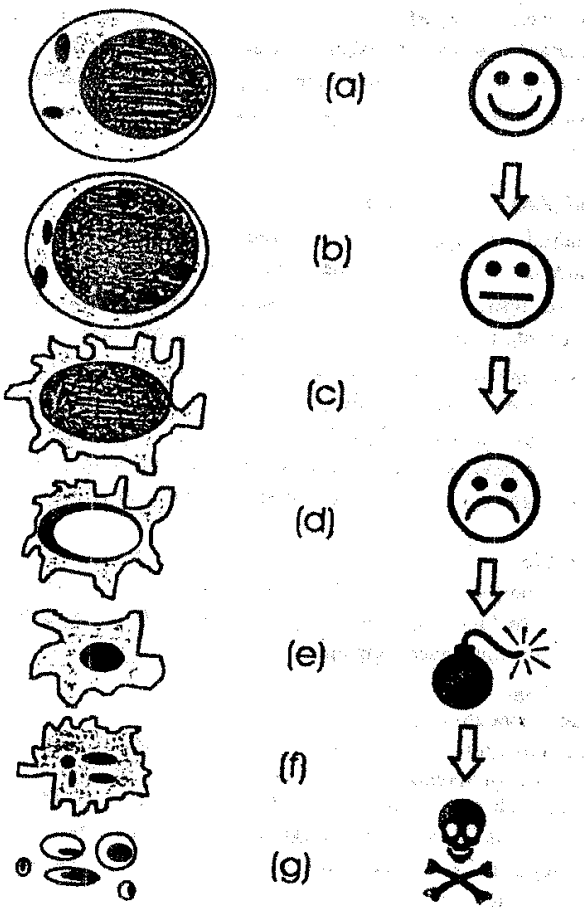


Figure no. 3
The main phases of apoptosis in lymphocytes: (a) normal lymphocyte; (b) decrease of nucleus/cytoplasm ratio; (c) shrinkage of cell and chromatin condensation; (d) chromatin collapses on the inner face of nuclear membrane; (e) the nucleus is transformed in a "black hole"; (f) kariorrhexis; (g) formation of apoptotic bodies.

Three phases of apoptosis: initiation, effector and degradation

- The process of apoptosis can be subdivided into at least three different phases. During the heterogenous **initiation phase**, cells receive apoptosis-triggering stimuli. Such death inducers include ligation of certain receptors or, in the case of obligate growth factor receptors, the absence of receptor occupancy. In addition, intervention on second messenger systems (Ca^{2+}, ceramide, kinases, phosphoinositolphosphates), suboptimal growth conditions (shortage of essential nutrients, hypoxia), mild physical damage (radiotherapy), and numerous toxins (reactive oxygen species, chemotherapy, and toxins stricto sensu) can induce apoptosis. Both these non-specific or receptor-mediated death induction involves a **stimulus dependent ('private') biochemical pathway**, and it is only after this initiation phase that **common pathways** come into action.
- It is generally assumed that the **effector phase** of apoptosis defines the "decision to die" at the "point-of-no-return" of the apoptotic cascade. It is at this level that the different private pathways converge into one (or few) common pathway(s) and that cellular processes (redox , expression levels of oncogene products including Bcl-2 related proteins) have still a decisive regulatory function.
- Once the cell has been irreversibly committed to death, the different manifestations classically associated with apoptosis such as DNA fragmentation become detectable. The **degradation phase** is similar in all cell types. It is characterized by the action of catabolic enzymes, mostly specific **proteases** (caspases, a family of cysteine proteases cleaving after Asp residues) and **endonucleases**, within the limits of a near-to-intact plasma membrane.

The crucial role of mitochondria in apoptosis

Mitochondria fulfill an essential role during the execution phase of apoptosis: the barrier function of either of the mitochondrial membranes is lost, leading to the dissipation of the inner transmembrane proton gradient and / or the release of intermembrane proteins such as cytochrome c via the mechanically disrupted outer membrane. These mitochondrial changes mark the 'point-of-no-return' and determine the fate of the cell. After dissipation of the proton gradient and /or release of cytochrome c (which disrupts the transfer of electrons between respiratory chain complexes III and IV), mitochondria lose their anti-oxidant function, produce superoxide anion, and provoke a bioenergetic catastrophe, culminating in cell death irrespective of the activation of caspases and endonucleases.

Altogether, present data are compatible with a general mechanism in which three phases can be distinguished: (i) a (mostly) *pre-mitochondrial phase* (induction phase) during which, depending on the apoptosis inducing stimulus, a large variety of signal transduction cascades or damage pathways can be activated; (ii) a *mitochondrial*

phase (effector phase) during which the mitochondrial membrane integrity is lost and the 'decision to die' is made; and (iii) a *post-mitochondrial* (degradation phase) during which soluble factors released by mitochondria activate catabolic hydrolases responsible for the apoptotic degradation of essential proteins and nuclear DNA.

PHASES OF APOPTOTIC PROCESS

Phase	Characteristics
Initiation (mostly pre-mitochondrial)	Numerous 'private' (the sequence of molecular events depends on the apoptosis-initiating stimulus) pathways are triggered via receptor-mediated signal transduction cascades or cellular damage. Some effector molecules converge on mitochondria.
Effector (mitochondrial)	Mitochondrial membrane function is perturbed at the levels of inner membrane and/or the outer membrane causing the release of intermembrane proteins into the cytosol. The bioenergetic consequence of these changes (cessation of anti-oxidant functiond and ATP generation) and/or the activation of caspases by intermembrane proteins engage in a feed-back amplification loop further compromising mitochondrial membrane function.
Degradation (post-mitochondrial)	Major changes in cellular physiology at all levels Plasma membrane: exposure of phosphatidylserine residues, outflow of K^+, later influx of Ca^{2+}, increase in permeability, and finally cytolysis Redox potentials: depletion of non-oxidized glutathione. hyperproduction of reactive oxygen species, oxydation of unsaturated lipids Caspases: activation of the caspase cascade and degradation of multiple structural and repair proteins in the cytosol, cytoskeleton and nucleus. Endonucleases: internucleosomal chromatin degradation

APOPTOSIS vs. NECROSIS: A COMPARISON

APOPTOSIS	NECROSIS
Kind of death: active	Kind of death: passive
Physiological or pathological (subnecrotic damage)	Accidental Always pathological
Timing: slow unfolding	Timing: fast unfolding
single cells selected	groups of cells destroyed
ATP required for the process	caused by ATP exhaustion
Susceptibility tightly regulated	Unregulated or poorly regulated
Plasma membranes intact until late stage	Membranes destroyed early
Cell volume: decreased; cell shrinkage	Cell volume: increased; cell swelling
Cell density: increased	Cell density: decreased
DNA degradation: early	DNA degradation: in the end
Characteristic biochemical and morphological features: *chromatin condensation (pyknosis) *regular DNA fragmentation (ladder pattern) *nuclear fragmentation (karyorrhexis)	No typical biochemical or morphological features
No inflammation	Inflammation

Morphologic features of apoptosis versus necrosis

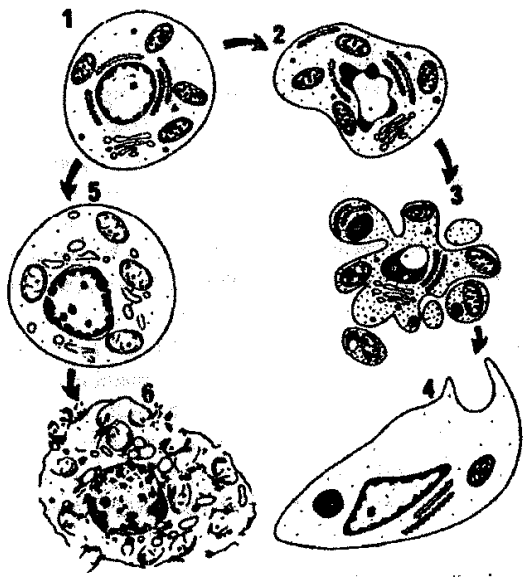


Figure no. 4

Diagram illustrating the sequential ultrastructure changes in apoptosis (right) and necrosis (left). A normal cell is shown at 1. The onset of apoptosis (2) is heralded by compaction and segregation of chromatin against the nuclear envelope and condensation of the cytoplasm. Rapid progression of the process (3) is associated with nuclear fragmentation and marked convolution of the cellular surfacewith the development of protuberances. The latter then separate to produce membrane-bound apoptotic bodies, which are phagocytosed and digested by the adjacent cells (4). Signs of necrosis include (5) clumping of chromatin into ill-defined masses, gross swelling of organelles, the appearance of floculent densities in the matrix of mitochondria, and later (6) membrane damage.

THE DUAL NATURE OF APOPTOSIS-REGULATING MECHANISMS

Apoptosis is controled by antagonistic mechanisms which involves gene interaction. There are antiapoptotic genes and genes which increase the susceptibility of cells to apoptotic stimuli. Either hyperexpression of apoptotic genes or underexpression of apoptosis resistance genes result in apoptotic death. The reverse situation endows the cells with the ability to by-pass death inducing messages. These

result in either uncontrolled cellular proliferation or increased life time of those cells usually destined to death.

ANTIAPOPTOTIC GENES

Bcl-2 is th prototype of a class of oncogenes which regulates apoptosis and may either promote cell survival or encourage cell demise. The relative amount of death agonists and antagonists from th Bcl-2 family constitues a regulatory rheostat whose function is determined, at least in part, by selective protein-protein interactions. Bcl-2 and its homologs insert into intracellular membranes including mitochondria, the endoplasmic reticulum and the nuclear envelope. Bcl-2-related molecules exert their apoptosis-regulatory effects via regulating mitochondrial alterations preceding the activation of apoptogenic proteases and nucleases. Via a direct effect on mitochondrial membranes, Bcl-2 prevents all hallmarks of the early stage of apoptosis including disruption of the inner mitochondrial transmembrane potential and the release of apoptogenic protease activators from mitochondria.

The death antagonistic and death promoting members of the Bcl-2 family function as potential oncogenes and tumour suppresor genes, respectively. Many tumours hyperexpress apoptosis-inhibitory or hypoexpress death-inducing members of the Bcl family.

Rb gene

The product of the Rb (pRb) gene is a nuclear phosphoprotein that regulates the cell cycle. It is expressed in every cell type examined, where it exists in an active underphosphorilated and inactive hyperphosphorilated state. It is proposed that in its active state Rb protein serves as a brake on the advancement of cells from G0/G1 to the S phase of the cell cycle. When the cells are stimulated to divide, the Rb protein is inactivated by phosphorilation, the brake is released, and the cell undergoes mitosis. In its hypophosphorilated form pRb prevents cell replication by binding, and then sequestering , transcription factors. Such factors include the product of the c-myc gene. Mutations of the Rb gene typically involve the transcription factor binding domain with subsequent uncontrolled cycling of cells because the acticity of transcription factors cannot be regulated. It has been revealed that the transforming proteins of several animal and human DNA viruses bind to the hypophosphorilated form of pRb rendering it functionally deleted.

PROAPOPTOTIC GENES

p53 is a nuclear phosphoprotein that regulates DNA replication, cell proliferation and cell death. p53 is known to act as a "molecular policeman" that prevents the propagation of genetically damaged cells. Under physiologic conditions P53 has a very short half-life and there is no evidence that this protein is required for

normal cell division. Once cells are exposed to mutagenic agents such as chemicals or irradiation p53 is stabilized through post-transational modifications and it accumulates within the nucleus. The accumulated p53 binds to DNA and causes cells to arrest in G_1 phase of the cell cycle. This reversible pause in cell cycling is welcome because it allows the cells time to repair the DNA damage inflicted by the mutagenic agent. If for some reason the repair mechanisms fail, p53 seems to sense the risk of allowing mutated cells to divide and triggers the cell death by apoptosis. With loss of normal p53 (common in many tumors) cells exposed to mutagenic agents replicate the damaged DNA, and thus mutations become fixed in the genome predisposing cells to additional mutations and, ultimately, to malignant transformation.

c-myc

The c-myc proto-oncogene is expresses in virtually all eukariotic cells and belongs to the early growth response genes which are rapidly induced when quiescent cells receive a signal to divide. Specific antisense nucleotides prevents the entry of cells into the S-phase. Following translation, the c-myc protein is rapidly translocated to the nucleus, it forms a heterodimer with another protein, called max. Next the c-myc/max complex binds to specific DNA sequences, presumably in the vicinity of genes that are essential for cell proliferation.

c-myc protein fulfills two apparently contradictory functions: it stimulates cell proliferation and it also increases the susceptibility to apoptosis-inducing stimuli. Oddly enough the molecular domains involved in transcription may also induce apoptosis. This discloses a common mechanism for these two pathways.

III.3. Physiologic and pathologic apoptosis

Therefore, apoptosis is thought to reflect for a wide range of physiologic and pathologic events including the following:

- The programmed destruction of cells during embriogenesis and metamorphosis.
- Hormone-dependent involution in the adult, such as endometrial cell breakdown during the menstrual cycle, ovarian follicular atresia in the menopause, and the regression of the lactating breast after weaning.
- Cell death in tumors, most frequently after therapy but also in tumors with active cell growth.
- Death of immune cells, both B and T lymphocytes after cytokine depletion, as well as the deletion of autoreactive T cells in the developing thymus. Autoimmune disorders seems to be the result of the absent apoptotic autoreactive clonal deletion.

- Cancer is frequently associated with the resistance of transformed cells to apoptotic stimuli.
- Pathologic atrophy of hormone-dependent tissues, such as prostatic atrophy after castration and loss of lymphocytes in the thymus after glucocorticoid administration.
- Pathologic atrophy in parenchimal organs after duct obstruction, such as occurs in the pancreas, parotid gland, and kidney.
- Cell death induced by cytotoxic T cells, such as in cellular immune rejection and graft- versus-host disease.
- Cell injury in certain viral diseases, as for example in viral hepatitis.
- Cell death produced by a variety of injurious stimuli that are capable of producing necrosis, but when given in low doses - including mild thermal injury, radiation, cytotoxic anticancer drugs, and possibly hypoxia - induce apoptosis.
- neurodegenerative disorders with neuronal loss are considered to be the result of the excessive apoptotic death
- aplastic anemia is also considered to be the result of apoptotic death of stem cells

I.5. PATHOPHYSIOLOGY OF INFLAMMATORY REACTION

Definition

In the first century AD Aurelius Celsius in his writings *De re Medicina* described inflamed tissues as being hot, swollen, red, and painful. About a century later, Galen added loss of function to the four *cardinal signs* of inflammation. Although a great deal of knowledge about inflammation has been accumulated since this first observations, much remains to be learned.

Inflammation is a reaction of tissues to the injury and comprises a complex series of vascular, humoral and cellular events at or near the site of injury. It is reasonable to regard inflammation as a process which attempts to eliminate offending agents or their effects. Restoration of structure and function of affected tissues is achieved to varying degree by *reparative processes*, which go hand in hand with inflammation. Inflammation tends to dominate the early events that follow injury, whereas repair begins at an early stage and assumes a major role in the later stages.

Inflammation

Inflammation is commonly caused by (1) micro-organisms, (2) physical trauma, (3) thermal injury, (4) radiation, (5) foreign bodies including dead tissue, and (6) immune reactions and (7) ischemia.

It is important to distinguish between inflammation and infection. Infection is the presence and replication of micro-organisms in the tissues. Infection often leads to inflammation, but this is not invariable. In cholera, for example, large numbers of pathogenic bacteria are present in close contact with intestinal epithelium, but there is no evidence of inflammation or damage to the mucosa. There is, however, severe derangement of intestinal mucosa cell function resulting from the enterotoxin elaborated by *Vibrio cholerae*. It should also be remembered that inflammation can be an immune reaction without the participation of micro-organisms, also micro-organisms themselves may stimulate immune reactions.

Although previously listed separately as causes of inflammation, infections and immune reactions have much in common. Infections tend to provoke immune reactions. The mediators of inflammation, especially the components of the complement system, are important in the genesis of many immune reactions. Lymphocytes, which are predominant cells in chronic inflammation, are a major component of the immune response.

The inflammatory processes caused by micro-organisms are complex and variable because of many biologically active substance involved. *Staphylococcus aureus*, for example, a common cause of skin and soft tissue inflammation, produces numerous extracellular enzymes, many of which are capable of modifying the basic inflammatory response, often to the advantage of the organism. *S. aureus* and other bacteria can produce leukocidins, which can rapidly kill the leukocytes that arrive on the scene to engulf them.

Inflammation can be classified as (1) acute, (2) chronic, or (3) granulomatous.

Acute inflammation short lived process developing in response to a single episode of injury. The duration of the process is usualy measured in hours or days, and its main characteristics are the exudation of fluid and plasma proteins (edema) and the imigration of leukocytes, predominantly neutrophils.

Chronic inflammation is prolonged – in response to continuous or repeated episodes of injury, and is associated histologically with the presence of lymphocytes and macrophages and the proliferation of blood vessels and connective tissue.

Granulomatous inflammation is a specific form of chronic inflammation that develops in response to certain specific agents such as mycobacteria and fungi.

Acute inflammation

Acute inflammation is a natural defense mechanism; it is a protective response of alive tissue. Most frequently is caused by infectious agents, heat and cold, or physical trauma. Despite the diversity of causes the early phases appear to be the same. The events evolve continuously, but they can be divided into those which are (1) vascular, (2) cellular and (3) metabolic. Common to these phases are many complex controlling mechanisms or mediators that involve a bewildering network of reactions.

Vascular events

The vascular events of acute inflammation take place in the microvascular circulation, which consist of arterioles, capillaries and venules. Blood flow into the capillary, bed is controlled by the smooth muscle in the arteriolar walls, which can act as a sphincter and adjust the amount of blood entering the capillaries, for example, during exercise.

The order of events as observed in experimental inflammation is a follows:

1. **Transient vasoconstriction**: it lasts seconds to minutes and may be neurogenic in origin.
2. **Vasodilation:** The initial vasoconstriction is followed be massive vasodilation in the arterioles and capillaries in the injured area.

a. This leads to postcapillary venule dilation and allows increased blood flow to the site (hyperemia), which is reflected clinically by heat and erythema – **the flare phenomenon.**

b. If intracapillary hydrostatic pressure exceeds the capillary bed tissue pressure, the resulting movement of fluid (i.e. transudate) into the tissue causes edema, which results in a wheal.

3. **Increased vascular permeability**. A release of chemical substances causes an increase in vascular permeability, with passage of plasma (i.e., colloid and water), resulting in further edema and vascular stasis. The increase in vascular permeability is due, in part, to widened junctions between vascular endothelial cells.

a. Effects of increased vascular permeability

1. The extravasated fluid that forms is an **exudate**, which has a higher specific gravity than the transudate that forms earlier in the inflammatory process. This is due to its high plasma protein and leukocyte content. Exudation of fluid from the capillaries to the injured area helps to dilute the toxic or irritating agent and brings antibodies, complement, leukocytes, and chemotactic substances to the area.

2. The loss of plasma due to the increased vascular permeability leads to vascular stasis and sluggish movement of the red cell through the microcirculation. Eventually, blood clots form in the small capillaries that supply the inflammed area, helping to localize the effects of the injury.

b. Types of increased vascular permeability

1. The **immediate transient response** involves small and medium size venules. Heat and histamine cause contraction of endothelial cells, resulting in widened intercellular gaps. This type is characteristic of type I hipersensitivity reactions.
2. An **immediate sustained response** is usually seen in *necrotizing injuries* and is due to direct damage to the endothelium by the injourious stimulus, as for example by severe burns or lytic bacterial infections. In most instances leakage starts immediate after injury and is sustained at a high level for sevearj hours until the damaged vessels are thrombosed or repaired. It affects venules, arterioles and capillaries alike. Endothelial cell detachement is often associated with platelet adhesion and trombosis.
3. A **delayed prolonged response** begins after a delay of 2 to 12 hours, lasts for several hours or even days, and involves venules as well as capillaries. Such leakage is caused, for example, by mild-to-moderate thermal injury, X- or ultraviolet radiation. The mechanism for such leakage is unclear. It may result from the direct effect of the injourious agent, leading to delayed cell damage (perhaps by apoptosis), or the effect of cytokines causing endothelial retraction, as described earlier.
4. **Leokocyte mediated endothelial injury**, leukocyte adhere to the endothelium relatively early in inflammation. As we shall see, such leukocytes may be activated in the process, relasing toxic oxygen species and proteolitic enzymes, which than cause endothelial injury and detachment – resulting in increased permeability.

c. The role of fluid *exudate*

Inflammatory exudate consists of protein derived from blood plasma. The high specific gravity (approximately 1.020) is result of presence of fibrinogen. Some of the effects of inflammatory exudate are as follows:

1. It contains fibrinogen, which is deposited as fibrin and which may contribute to forming a barrier against further spread of infection.
2. It may help dilute bacterial or other toxins.
3. It contains complement proteins and sometimes specific antibodies that can have a bactericidal effect.
4. It may contain opsonins, which enhance phagocytosis by leukocytes.
5. It can act as a vehicle for antimicrobial drugs.

A *transsudate*, on the other hand, is a fluid of lower specific gravity (1.010 or less) that escapes from a tissue or membrane. It contains little or no fibrinogen, and thus its composition is very similar to serum. It is usually the result of mild injury to the tissue, which allows fluid and smaller blood protein molecules to escape to the smaller gaps in the capillary endothelium.

Cellular events

Leukocytes reach and deal with an infection or other injury as a result of a sequence of events. The sequence of events in the journey of leukocytes from the lumen to the interstitial tissue can be divided into the following steps:

(1) in the lumen: margination, rolling and adhesion;
(2) transmigration across the endothelium (also called diapedesis);
(3) migration in the interstitial tissues toward a chemotactic stimulus;
(4) phagocytosis;
(5) release of leukocyte products.

1. Margination, rolling and adhesion

During the vascular stasis stage of hyperemia, as blood flow slows, leukocytes (principally neutrophils and monocytes) fall out of the central column and assume a peripheral position along the endothelial surface. This initial process called **margination**, is caused largely by changes in hemodinamic conditions engendered by low and slow blood circulation. Subsequently, individual and then rows of leukocytes tumble slowly along the endothelium and adhere transiently (a process called **rolling**), finally coming to rest at some point where they adhere firmly (resembling "pebbles or marbles over which a stream runs without disturbing them"). In time, the endothelium can be virtually lined by white cells, an appearance called **"pavementing"**.

2. **Diapedesis** (also called **emigration**) refers to the process by which leukocyte migrate from blood vessels.

a. Leukocytes develop pseudopods and emigrate, without accompanying loss of fluid, through gaps between the endothelial cells. The migration is purposeful, directed and ameboid, and it occurs without endothelial cell contraction.

- **Neutrophils** are the first to emigrate outside the vascular compartments. They are short-lived, with a life span of 24 to 48 hours, and they contain a chemotactic factor for monocytes.
- **Monocytes** follow neutrophils into the site of inflammation, apparently on cue from the chemotactic factor elaborated by neutrophils. Monocytes are refered to as macrophages or **histiocytes** after emigrating.

However, there are exceptions to this patterns of cellular exudation. In certain infections, for example those produced by **Pseudomonas organisms**, neutrophils predominate over 2 to 4 days; in viral infections, lymphocytes may be the first cell to arrive; in some hypersensitivity reactions, eosinophilic granulocytes may be the main cell type.

b. All leukocytes-neutrophils, basophils, eosinophils, lymphocytes, and monocytes- emigrate in the same manner. Occasionally, passive emigration of red cells may accompany leukocyte diapedesis.

We shall now examine the molecular mechanisms of each of these steps.

It is now clear that leukocytes adhesion and diapedesis are determined largely by binding of complementary adhesion molecules on the leukocyte and endothelial surfaces (like a key in the lock), and that chemical mediators – chemoattractants and certain cytokines – affect these processes by modulating the surface expression or avidity of such adhesion molecules.

The adhesion receptors involved belong to three molecular families: the **selectins**, the **immunoglobulins**, and the **integrins**. These molecules are modulated to induce adhesion in inflammation as follows:

1. *Redistribution of adhesion molecules to the cell surface*. P-selectin, for example, is normally present in the membrane of specific intracytoplasmatic endothelial granules. On stimulation by mediators such as histamine, thrombine and platelet activating factor (PAF), P-selectin is rapidly distributed to the cell surface, where it can bind the leukocytes. Studies suggest that this process may be particularly important in early leukocyte rolling on endothelium.
2. *Induction of adhesion molecules and endothelium*. Some inflammatory mediators and particularly cytokines (IL-1 and TNF), induce the synthesis and surface expression of endothelial adhesion molecules.
3. *Increased avidity of binding*. The mechanisms most relevant to the binding of integrins. For example, LFA-1 is normally present on leukocytes – neutrophils, monocytes and lymphocytes – but does not adhere to its ligand ICAM-1 on endothelium. When neutrophils are activated by chemotactic agents or other stimuli, the LFA-1 is converted from a state of low – to high-affinity binding toward ICAM-1, owing to a conformational change in the molecule.

Based on such studies, a currently popular scenario for neutrophils adhesion and transmigration in acute inflammation postulates the following steps:

1. First, there is initial rapid and relatively loose adhesion that accounts for rolling, involving mainly the naturally occuring P-and L-selectins and, in cytokine-induced endothelium, E-selectin;

2. The leukocytes are then activated by agents made by endothelium and other cells or emanating from the site of injury, to increase the avidity of their integrins.
3. They then bind stably to the endothelium, largely through the β_2 integrin-ICAM-1 pathway, and undergo transmigration.

The most telling proof of the importance of adhesion molecules is the existence of clinical genetic deficiencies in the leukocyte adhesion proteins, which are characterized by impaired leukocyte adhesion and recurrent bacterial infections.

3. Chemotaxis and activation. Chemotaxis is the process by which leukocytes are directed to the site of the injury as locomotion oriented along a chemical gradient. Both **endogenous and exogenous** substances can act as chemoattractants. The most common exogenous agents are bacterial products. Endogenous chemical mediators include:

- Components of the **complement system**, particularly C5a;
- **Products of the lipoxygenase pathway**, mainly leukotriene B_4 (LTB_4);
- **Cytokines**, particularly those of the IL-8 family.

In addition to stimulating locomotion, many chemotactic factors, particularly in high concentrations, induce other responses in the leukocytes reffered as **leukocyte activation**. Such responses, which can also be induced by phagocytosis and antigen-antibody complexes include the following:

- Production of arachidonic acid methabolites;
- Degranulation and secretion of lysosomal enzymes, and activation of the oxidative burst;
- Modulation of leukocyte adhesion molecules.

A newly appreciated phenomenon in leukocyte activation is **priming**, denoting an increased rate and extent of leukocyte activation by exposure to a mediator that itself causes little activation. The cytokine TNF, in particular, markedly increases leukocyte activation by other chemotactic agents, accounting for its powerful *in vivo* effects.

4. Phagocytosis involves three distinct but inter-related steps: **recognition and attachment** of the particle to be ingested by the leukocytes; its **engulfment**, with subsequent formation of a phagocytic vacuole; and **killing or degradation** of the ingested material.

- **Recognition and attachement**. Most microorganisms are not recognized until they are coated by naturally occuring factors called opsonins. The two major opsonins are:

(1) the Fc fragment of immunoglobulin G (IgG), presumably naturally occuring antibody against the ingested particle;

(2) C3b, the so called "opsonic fragment of C3".

The corresponding receptors on leukocytes are FcγR which recognize the Fc fragment of IgG, and complement receptors.

- **Engulfment.** Binding of the opsonized particle to the FcγR is sufficient to trigger engulfment, which is markedly enhanced in the presence of Crs. During engulfment, extensions of the cytoplasm (pseudopods) flow around the object to be engulfed resulting in complete enclosure of the particle within a phagosome created by the cytoplasmic membrane of the cell. The limiting membrane of this phagocytic vacuole then fuses with the limiting membrane of a lysosomal granule, resulting in the granule discharging into the paholysosome.
- **Killing or degradation.** Bacterial killing is accomplished largely by oxygen dependent mechanisms. Phagocytosis stimulates a burst in oxygen consumption, gluycogenolysis, increased glucose oxidation via the hexose-monophosphate shunt and production of reactive oxygene metabolites.

The generation of oxygen metabilites is due to the rapid activation of an oxidase (NADPH oxidase), which oxidizes NADPH and, in the process reduces oxygen to superoxyde ion $O_2^{\cdot -}$.

Superoxide is then converted into H_2O_2. The quantities of H_2O_2 produced in the phagolysosome are insufficient to induce effective killing of bacteria. However, the azurophilic granules of neutrophils contain the enzyme myeloperoxidase (MPO), which, in the presence of a halide such as Cl^- converts H_2O_2 to $HOCl^-$. The latter is an antimicrobial agent that destroys bacteria by halogenation (in which the halide is bound covalently to cellular constituents) or by oxidation of proteins and lipids (lipid peroxidation).

The importance of oxygen-dependent bacterial killing is shown by existence of a group of congenital disorders in bacterial killing called **chronic granulomatous disease (CGD)**, which made pacients susceptible to recurrent bacterial infections.

Bacterial killing could also occur in the absence of the oxidative burst, by substances in the leukocyte granules. These include:

- **bactericidal permeability increasing protein (BPI)**, a highly cationic granule-associated protein that causes phospholipase activation, phospholipid degradation and increase permeability in the outer membrane of the microorganisms;
- **lysosime**, which hydrolizes the muramic acid-N-acetyl-glucosamine bond, found in the glycopeptide coat of all bacteria;
- **lactoferin**, an iron binding protein present in specific granules;
- **major basic protein (MBP)**, a cationic protein of eosinophils, which has limited bactericidal activity but is cytotoxic to many parasites and

- **defensins**, cationic arginine-rich granule peptides that are cytotoxic to microbes.

- **Release of leukocyte products.** The membrane perturbations that occur in neutrophils and monocytes during chemotaxis and phagocytosis result in the release of products not only within phagolysosome but also potentially into the extracellular space. The most important of these substances are:
  - lysosomal enzymes, present in the neutrophil granules;
  - oxygen derived active metabolites and
  - products of arachidonic acid metabolism, including prostaglandines and leukotrienes.

These products are powerful mediators of endothelial injury and tissue damage and amplify the effects of the initial inflammatory stimulus. Thus, if persistent and unchecked, the leukocyte infiltrate itself becomes the offender, and indeed leukocyte dependent tissue injury underlies many human diseases, such as rheumathoid arthritis and certain forms of lung disease.

Summary of the acute inflammatory response

The vascular phenomena are characterized by increased blood flow to the injured area, resulting mainly from arteriolar dilatation and opening of the capillary beds. Increased vascular permeability results in the accumulation of protein-rich extravascular fluid, which form the exudate. Plasma proteins leave the vessels, most commonly through widened interendothelial cell junctions of venules or by direct endothelial injury. The leukocytes, initially predominantly neutrophils, adhere to the endothelium via adhesion molecules, transmigrate across the endothelium, and migrate to the site of injury under the influence of chemotactic agents. Phagocytosis of the offending agent follows, which may lead to the death of the microorganism. During chemotaxis and phagocytosis, activated leukocytes may release toxic metabolites and proteases extracellulary, potentially causing tissue damage.

Chemical mediators of inflammation

Having described the events in acute inflammation. We can turn now to discuss the chemical mediators that account for these events. Here we review generak principles and highlight some of the more important mediators.

- *Mediators originate either from plasma or from cells.* Plasma derived mediators (e.g. complement) are present in plasma in *precursors forms that must be activated*, usually by a series of proteolitic cleavages, to acquire their

biologic properties. Cell-derived mediators are normally *sequestred (preformed) in intracellular granules* (e.g. histamine in mast cell granules) that have to be secreted or *are synthesized de novo* (e.g. prostaglandins) in response to a stimulus. The major cellular sources are platelets, neutrophils, monocytes /macrophages, and mast cells.

- Most mediators perform their biologic activity by initialy *binding to specific receptors on target cells*. Some, however, have direct enzymatic activity (e.g. lysosomal proteases) or mediate oxydative damage (e.g. oxygen metabiolites).
- A chemical mediator can stimulate the release of mediators by target cells themselves. These secondary mediators may be identical or similar to the initial mediators but may also have opposing activities. They provide mechanisms for amplifying – or in certain instances counteracting – the initial mediator action.
- Once activated and released from the cell, most of these mediators are short lived. They quickly decay (e.g. arachidonic acid metabolites) or are inactivated by enzymes (e.g. kynininase inactivates bradykinin), or they are otherwise scavanged (antioxidants scavange toxcic oxygen metabolites) or inhibited (e.g. complement inhibitors). There is thus a system of check and balanced in the regulation of mediator action.
- most mediators may have harmful effects.

Cell-derived mediators

A. PREFORMED MEDIATORS

Vasoactive amines

1. Histamine. The richest sources of histamine are the mast cells that are normally present in the connective tissue adjacent to blood vessels and in blood basophils and platelets.

Preformed histamine is present in mast cell granules and is released by mast cell degranulation in response to a variety of stimuli:

- physical injury such as trauma, cold, and heat;
- immune reactions involving binding of antibodies to mast cells;
- fragments of complement called anaphilatoxins (C3a and C5a);
- histamine releasing proteins derived from leukocytes;
- neuropeptides (e.g, substance P);
- cytokines (IL-1, IL-8).

In humans, histamine causes dilatation of the arterioles and increases vascular permeability of the venules. It is considered to be the principal mediator of the

immediate phase and increases vascular permeability of the venules. It is considered to be the principal mediator of the immediate phase and increased vascular permeability, causing venular endothelial contraction and widening of the interendothelial cell junctions. It acts on the microcirculation via H_1 receptors.

2. Serotonin is a second preformed vasoactive mediator with actions similar to those of histamine. It is present in platelets and enterochromaffin cells.

3. Lysosomal constitutes of leukocytes

Neutrophils and monocytes contain lysosomal: granules, which when released may contribute to the inflammatory response. Neutrophils exhibit two main types of granules. The smaller **specific** (or secondary) granules contain lactoferrin, lysozyme, alkaline phosphatase, the components of NADPH oxidase involed in respiratory burst, the intracytoplasmatic pool of integrinss, and a collagenase. The large **azurophil** (or primary) granules contain bactericidal factors (lysozime, defensins), acid hydrolases, and a variety of neutral proteases (elastase, nonspecific collagenases). These enzymes are either released after cell death or secreted by a variety of mechanisms. There are, however, differences in the mobilization of specific and azurophil granules. The specific granules are secreted more readily and by low concentrations of agonists, while the more potenatially destructive azurophil granules release their contents primarily within the phagosome and require very high levels of agonists to be released extracellularly.

Acid proteases degrade proteins at an acid pH. Their most likely action is to degrade bacteria and debris within the phagolisosomes, where and acid pH is readily reached. **Neutral proteases**, on the other hand, are capable of degrading various extracellular components. These enzymes can attack collagen, basement membrane, fibrin, elastin, and cartilage, resulting in tissue destruction *characteristic of purulent and deforming inflammatory processes*. Neutral proteases can also cleave C3 and C5 directly, releasing anaphylatoxins and release a kinin-like peptide from kininogen.

Lysosomal constituents thus have numerous effects. The initial leukocytic infiltration, if unchecked, can potentiate further increases in vascular permeability, chemotaxis, and tissue damage. These harmful proteases, however, are held in check by a system of **antiproteases** in the serum and the tissue fluids. Foremost among these is **alpha$_1$-antitrypsin**, which is major inhibitor of neutrophilic elastase. A deficiency of these inhibitors may lead to sustained action of leukocyte proteases, as in the case in patients with alpha$_1$-antitrypsin deficiency.

Alpha$_2$-macroglobulin is another antiprotease found in serum and various secretions.

B. SYNTHETIZED DE NOVO

1. Arachidonic acid (AA) metabolites: prostaglandins and leukotriens (Eicosanoids)

Arachidonic acid is a 20 carbon polyunsaturated fatty acid that is derived directly form dietary sources or by conversion from the essential fatty acid *linoleic acid*. It does not occur free in the cell but it is normally esterified in membrane

phospholipids. It is released from phospholipids through the activation of the cellular phospholipases by mechanical, chemical, and physicakl stimuli or by other mediators (e.g. C5a).

A metabolism proceeds along one of the two major pathways named after the enzymes that initiate the reactions.

- The **cyclooxygenase pathway** leads to the generation of **prostaglandins.** These include PGE_2, PGD_2, $PGF_{2\alpha}$, PGI_2 (prostacyclin), and tromboxane (TxA_2), each of which is derived by the action of a specific enzyme. Prostacyclin is a vasodilator and a potent inhibitor of platelet aggregation. TxA_2 (platelets contain the enzyme tromboxane synthetase) is a potent platelet aggregating agent and vasoconstrictor. PGD_2 is the major metabolite of the cyclooxygenase pathway in mast cells; along with PGE_2 and PGF_2 (which are more widely distributed) it causes vasodilatation and potentiates edema formation.

  Aspirin and nonsteroidal anti-inflammatory agents, such as indomethacin, inhibit cyclooxygenase and thus inhibit prostaglandin synthesis. Lipoxygenase, however, is not affected by these anti-inflammatory agents.

- In the **lipoxygenase pathway**, 5-lipoxygenase is the predominant enzyme in neutrophils, and the metabolites derived by its actions are the best characterized. The main product, 5-HETE, which is chemotactic for neutrophils, is converted into a family of compounds collectively called **leukotrienes.** LTB_4 is potent chemotactic agent and causes aggregation of neutrophils. LTC_4, LTD_4 and LTE_4 cause vasoconstriction, bronchospasm, and increase vascular permeability.

Eicosanoids can mediate virtually every step of acute inflammation:

- *Prostaglandin E* and *prostacyclin* are important mediators of inflammatory **vasodilatation.** They also markedly potentiate the permeability – increasing and chemotactic effects of other mediators.
- *Leukotrienes C_4, D_4 and E_4* cause intense **vasoconstriction** and **increase vascular permeability.** The vascular leakage, as with histamine, is restricted to venules. They are also potent **bronhoconstrictors.**
- *Leukotriene B_4* causes aggregation and adhesion of leukocytes to venular endothelium and is a powerful chemotactic agent.
- The prostaglandins are also involved in the pathogenesis of **fever** and **pain** in inflammation. PGE_2 causes a marked increase in pain produced by intradermal injection of suboptimal concentrations of histamine and bradykinin and interacts with cytokines in causing fever during infections.

- Variations in AA metabolism may account for some of beneficial effects of fish oil. Diet rich in fish oil contain *essential fatty acid of the ω 3 variety* rather than ω 2 linoleic acid found in most animal or vegetable fat. The ω 3 fatty acids serve as poor substrates for conversion to active metabolites of cyclooxygenase and, particularly, the lipoxygenase series. Such diets inhibit platelet aggregation and thrombosis and prevent certain inflammatory processes.

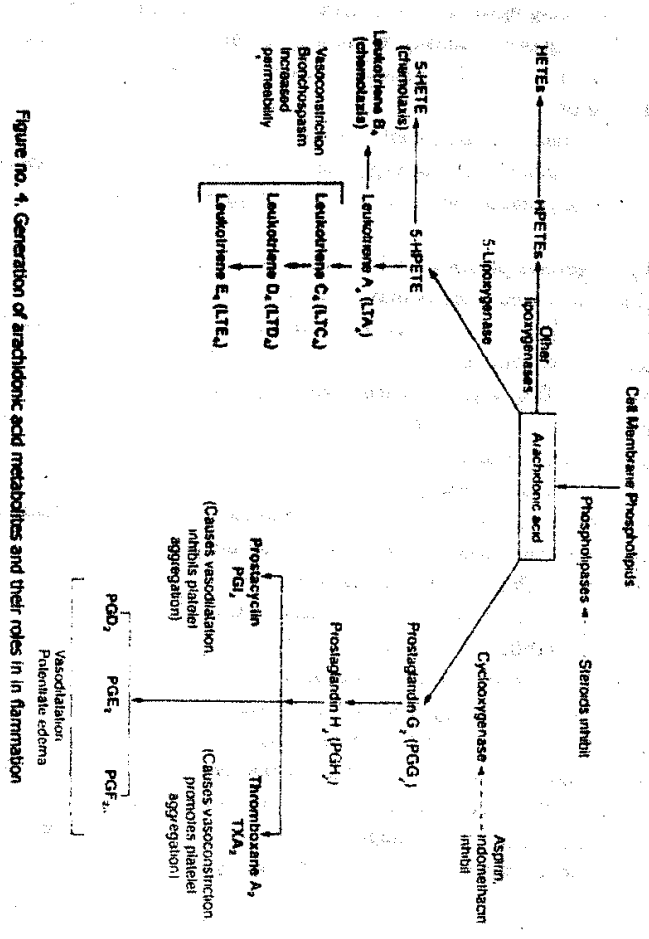


Figure no. 4. Generation of arachidonic acid metabolites and their roles in in flammation

2. Platelet-activating factor (PAF)

PAF is another phospholipid-derived mediator synthesized from membrane phospholipases. In addition to platelet stimulation, PAF causes vasoconstruction and bronhoconstriction, and at extremely low concentrations it induces vasodilatation and increase vascular permeability with a potency 100 to 10,000 times greater than of histamine. PAF also causes increased leukocyte adhesion to endothelium (by enhancing leukocyte integrin binding), chemotaxis, degranulation, and the oxidative burst.

Thus, PAF can elicit most of the cardinal features of inflammation. A variety of cell types, including basophils, neutrophils, monocytes, and endothelial cells, can elaborate PAF.

PAF acts directly on target cells via specific receptors, but it also boosts the synthesis of other mediators, particularly eicosanoids, by leukocytes and other cells.

3. Cytokines

Cytokines are polipeptides produced by many cell types (but principally activated lymphocytes and macrophages) that modulate the function of other cell types long known to be involved in cellular immune responses, these products have addition effects that play important roles in the inflammatory response.

The main cytokines that mediate inflammation are IL-1, TNF (α and β), and the IL-8 family.

IL-1 and TNF share many biologic properties. They are produced by activated macrophages, TNF-β by activated T cells, and IL-1, by other cell types as well. Their secretion can be stimulated by endotoxin, immune complexes, toxins, physical injury, and a variety of inflammatory processes.

Like growth factors, **they induce their effects in three ways**: they can act on the same cell that produces them (an **autocrine effect**), on cells in immediate vicinity (as in limph nodes and joint spaces; a **paracrine effect**); or systemically, as with any other hormone (**endocrine effect**).

Their most important actions in inflammation are their effects on endothelium, leukocytes and fibroblasts, and induction of the systemic *systemic acute-phase reactions*. (Fig. 5)

In endothelium they induce a spectrum of changes – mostly regulated at the level of gene transcription – reffered to as endothelial activation. In particular, they induce the synthesis of endothelial adhesion molecules, other cytokines, growth factors, eicosanoids, and nitric oxide and increase surface thrombogenicity of the endothelium. TNF also causes aggregation and ***priming*** of neutrophils, leading to augmented response of these cells to other mediators, and release of proteolitic enzymes from the mesenchymal cells, thus contributing to tissue damage.

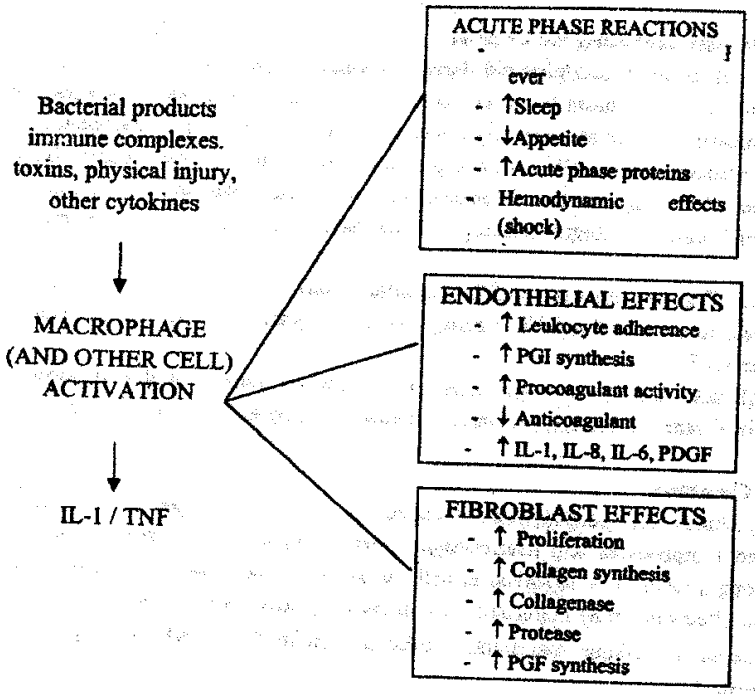


Figure no. 5

Major effects of interleukin IL-1 and tumor necrosis factor (TNF) in inflammation

IL-8 is a small polypeptide secreted by activated macrophages and other cell types (e.g. endothelial cells) that is a powerful **chemoattractant** and activator of neurophils, with limited action on monocytes and eosinophils. Its most important inducers are other cytokines, mainly IL-1 and TNF-α. It belongs to a family of structurally similar small proteins, now called **chemokines**. These include, in addition to IL-8, **platelet factor-4 (PF4)** with chemotactic activity for neutrophils, monocytes and eosinopjils and with histamine-realising activity for mast cells; **monocyte chemaattractant protein (MCP-1)**, a chemotactic and activating agent that is fairly specific for monocytes, and **RANTES**, which is chemotactic for thymocytes. The chemokines bind to a family of receptors, called **serpentines.**

Both IL-1 and TNF (as well as IL-6) also induce the systemic acute phase responses associated with infection or injury, including fever, the production of slow-wave sleep, the release of neutrophils into circulation, the release of adrenocorticotropic hormone (ACTH) and corticosteroids, and particularly with

regard to TNF, the hemodynamic effects of septic-hypotension, decreased vascular resistance, increased heart rate, and decreased blood pH.

4. Nitric Oxide

It is a soluble gas that is produced not only by endothelial cells but also by macrophages and specific neurons of the brain. *It is synthetized from L-arginine, molecular oxygen, and NADPH by the enzyme nitric oxide synthase (NOS).* There are two types of NOS. In endothelial cells an neurons, NOS is present constitutively and can be activated rapidly by an increase in cytoplasmic calcium ions in the presence of calmodulin. Influx of calcium in these cells leads to a rapid production of NO. In contrast, macrophage NOS is induced, when macrophages are activated by cytokines (e.g. IFN-γ) or other agents; no intracellular increase in calcium is necessary.

In addition to vascular smooth muscle relaxation, NO plays other important roles in inflammation, it reduces platelet aggregation and adhesion. The NO produced by macrophages, acting as a free radical, is cytotoxic to certain microbes and tumor cells. It can react with superoxyde to form the strong oxidant nitrogen dioxide and the highly reactive hydroxyl radical. Uncontrolled NO production by activated macrophages in septic shock can lead to massive peripheral vasodilatation and shock, and NO has been also been implicated in a variety of inflammatory diseases. Inhibitors of NO production are now being tested clinically and have been shown, for example, to reduce the size of ischemic brain infarcts.

5. Oxygen derived free radicals

These metabolites may be released extracellularly from leukocytes after exposure to chemotactic agents, immune complexes, or a phagocytic challenge. The production is dependent on the activation of the NADPH oxidative system and generation of superoxide. Superoxide, in turn, is converted to H_2O_2, OH ·, and, by combining with NO, to toxic NO derivates. They are implicated in the following responses:

- Endothelial cell damage, with resultant increased vascular permeability;
- Inactivation of antiproteases, such as alpha-antitrypsin. This leads to unpposed protease activity, with increased destruction of ECM.

Serum, tissue fluids, and target cells posses antioxidant mechanisms that detoxify these potentially harmful oxygen-derived radicals. These antioxidants include: (1) the copper containing serum protein **ceruloplasmin**, (2) the iron free fraction of serum **transferrin**, (3) the enzyme **superoxide dismutase**, which is found and can be activated in a variety of cell types, (4) the enzyme **catalase**, which detoxifies HO, and (5) **glutathione peroxidase**, another powerful H_2O_2 detoxifier.

Thus, the influence of oxygen-derived free radicals in any given inflammatory reaction depends on the balance between the production and the inactivation of these metabolites by cells and tissues.

Most likely mediators in inflammation

VASODILATION
Prostaglandins
Nitric oxide
INCREASED VASCULAR PERMEABILITY
Vasoactive amines
C3a and C5a (through liberating amines)
Bradykinin
Leukotrienes C_4, D_4, E_4
PAF
CHEMOTAXIS, LEUKOCYTE ACTIVATION
C5a
Leukotriene B_4
Bacterial products
Cytokines
FEVER
IL-1, IL-6, TNF
Prostaglandins
PAIN
Prostaglandins
Bradykinin
TISSUE DAMAGE
Neutrophil and macrophage lysosomal enzymes
Oxygen metabolites
Nitric oxide

Plasma derived mediators proteases

There are three interrelated factors: the *complement, kinin, and cloting systems.*

1. The complement system

The complement system consist of 20 component proteins which are found in greatest concentration in plasma. This system functions in immunity for defense against microbial agents, culminating in lising microbes by the so called membrane attack complex (MAC). In the process, a number of complement components are elaborated that cause increase vascular permeability, chemotaxis and opsonization (fig. 6).

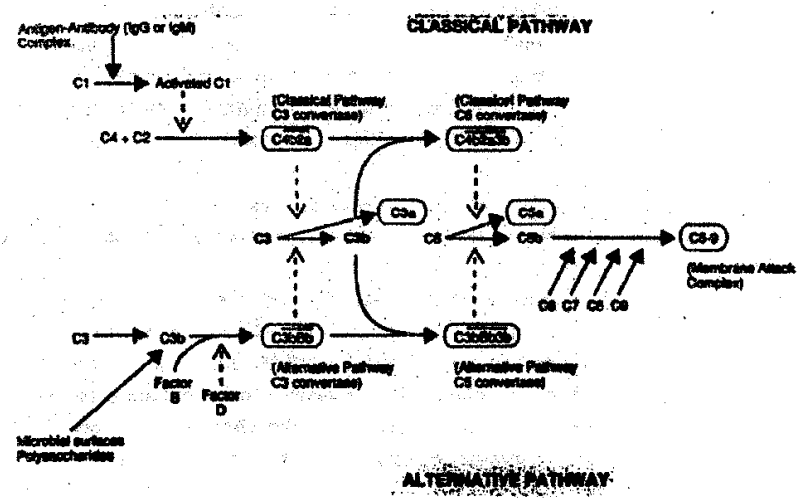


Figure no. 6. Complement activation

Complement components present as inactive forms are numbered C1 through C9. The most critical step in the elaboration of the biologic functions of complement is the activation of the third component C3. Cleavage of C3 can occur by the so-called classical pathway, which is triggered by fixation of C1 to antibody (IgG or IgM) combined with antigen, or through the alternative pathway, which can be triggered by microbial surfaces (e.g. endotoxins), aggregated IgA, complex polissacharides, endotoxins, cobra venom, and so forth. The alternative pathway involves the participation of a distinct set of serum components called the properdin system (properdin [P], factors B and D). Whichever pathway is involved, C3 convertase splits C3 into two critical fragments – C3a, which is released, and C3b. C3b then binds to the fragments to form C5 convertase, which interacts with C5 to release C5a and initiate the assembly of the membrane attack complex (C5-C9). MAC causes lysis by initial hydrophobic binding to the lipid bilayer of target cells, eventually forming transmembrane channels.

Complement derived factors affect a variety of phenomena in acute inflammation:

- **Vascular phenomena. C3a, C5a, and, to a small extent, C4a (called anaphylatoxins) are the split products of the corresponding complement components. They increase vascular permeability and cause vasodilatation**

mainly by releasing histamine from mast cells. C5a also activates the lipoxigenase pathway of arachidonic acid (AA) metabolism in neutrophils and monocytes, causing further release of inflammatory mediators.

- Leukocyte adhesion, chemotaxis and activation. C5a is a powerful chemotactic agent for neutrophils, monocytes, eosinophils and basophils. It also increases the adhesion of leukocytes to endothelium by activating the leukocytes and increasing the avidity of surface integrins to their endothelial ligand.
- Phagocytosis. C3b, when fixed to the bacterial cell wall, act as an opsonin and favor phagocytosis by neutrophils and macrophages which bear cell surface receptors for C3b.

Among the complement components, C3 and C5 are the most important inflammatory mediators. Their significance is further enhanced by the fact that, in addition to the mechanism discussed above, C3 and C5 can be activated by several proteolitic enzymes present within the inflammatory exudate. These include plasmin and lysosomal enzymes released from neutrophils. Thus, the chemotactic effect of complement and the complement activating effects of neutrophils can set up a self-perpetuating cycle of neutrophil emigration.

The kinin system

The kinin system is directly by contact (surface) activation of Hageman factor (factor XII of the intrinsic clotting pathway). The kinin system results in the ultimate release of the vasoactive nonapeptide **bradykinin**, a potent agent that increase vascular permeability. *Bradikinin also causes contraction of smooth muscle, dilation of blood vessels, and pain when injected into the skin.* The cascade that eventually produces kinin is shown in the fig. 7. It is triggered as noted by activation of Hageman factor by contact with negatively charged surfaces, such as collagen and basement membranes. A fragment of factor XII (prekallikrein activator or factor XIIa) is produced and this converts plasma **kallikrein** into an active proteolitic form, the enzyme kallikrein. The latter cleaves a plasma glycoprotein precursor, **high-molecular-weight kininogen (HMWK)**, to produce bradykinin (HMWK also acts as a cofactor or catalist in the activation of Hageman factor). The action of bradykinin is short lived because it is quickly inactivated by an enzyme called **kininase**. *Of importance is that kallikrein itself is a potent activator of Hageman factor allowing for autocatalitic amplification of the initial stimulus.* Kallikrein has chemotactic activity, and it also directly converts C5 to C5a.

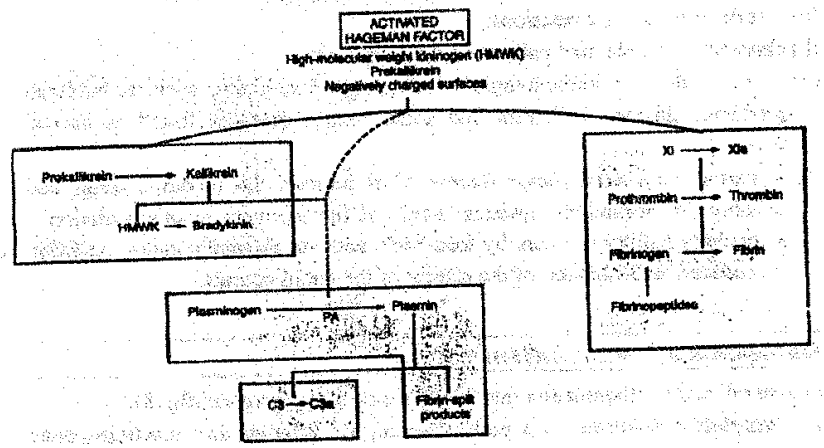


Figure no. 7. Involvement of clotting and fibrinolytic system in inflammation

The clotting system

The clotting system is a series of plasma proteins that can also be activated by Hageman factor. The final step of the cascade is the conversion of fibrinogen to fibrin by action of thrombin. During this conversion, **fibrinopeptides** are formed, which induce increased vascular permeability and chemotactic activity for leukocytes. **Thrombin** also has inflammatory properties, including causing increased leukocyte adherence and fibroblast proliferation.

The **fibrinolitic system** contributes to the vascular phenomena of inflammation in several ways. Plasminogen activator (released from endothelium, leukocytes and other tissues) cleaves plasminogen, a plasma protein that binds to the evolving fibrin clot to generate **plasmin**, a multifunctional protease. (Kallikrein and activated Hageman factor can also convert plasminogen to plasmin in vitro, but the physiologic significance of this is uncertain). Plasmin is important in lysing fibrin, but in the context of inflammation it also cleaves C3 to produce C3 fragments, and it degrades fibrin to form "fibrin split products", which may have permeability – inducing properties.

From discussion of the complex mediators generated by the kinin, clotting and complement system, a few general conclusions can be drawn:

- *Bradikinin. C3a and C5a (as mediators of increased vascular permeability), and C5a (as the mediator of chemotaxis)*, and *thrombin* which have effects on many cell types) are the most likely to be important *in vivo*.

- *C3 and C5* can be generated by three different groups of influences:

(a) classic immunologic reactions;

(b) alternative complement pathway activation, and

(c) agents with little immunologic immunologic specificity, such as bacterial products, plasmin, kallikrein and some serine proteases found in normal tissue.

- *Activated Hagemann factor (factor XIIa)* initiates the clotting, kinin, and possibly the fibrinolytic systems. Some of the products of this initiation – particularly kallikrein – can, by feed-back, activate Hageman factor, resulting in profound amplification of the effects of the initial contact.

Outcomes of acute inflammation

In general, acute inflammation may have one of four outcomes (fig. 8).

1. **Complete resolution.** In a perfect world, all inflammatory reactions, once they have succedeed in neutralizing the injurious stimulus, should end with restoration of the site of acute inflammation to normal. This is called resolution and is the usual outcome when the injury is limited or short-lived of where there has been little tissue distruction. Resolution involves neutralization of the chemical mediators, with subsequent return of normal vascular permeability, cessation of leukocyte infiltration, and finally removal of edema fluid and protein, leukocytes, foreign agents and necrotic debris from the battleground. Lymphatics and phagocytes play a role in these events.

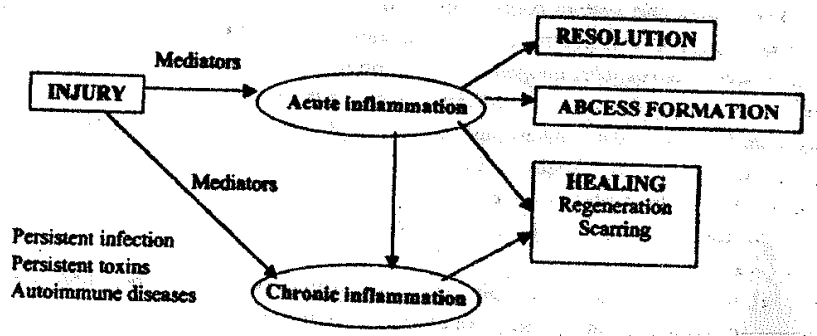


Figure no. 8
Outcomes of acute inflammation

2. **Healing by connective tissue replacement (fibrosis)** occurs after substantial tissue distruction, or when the inflammatory injury occurs in tissues that do not regenerate, or where is abundant fibrin exudation. When the fibrous exudate in tissues or serous cavities (pleura, peritoneum) cannot be adequately resorbed, connective tissue grows into the area of exudate, converting it into a mass of fibrous tissue – a process also called **organisation.**
3. **Abcess formation,** which occurs particularly in infections with pyogenic organisms.
4. Progression of the tissue response to **chronic inflammation,** may follow acute inflammation, or the response may be chronic almost from the onset. Acute to chronic transition occurs when the acute inflammatory respons cannot be resolved, owing either to the persistence of the injourious agent or to some interference in the normal process of healing. For example, bacterial infection of the lung may begin as a focus of acute inflammation (pneumonia), but its failure to resolve may lead to extensive tissue distruction and formation of a cavity in which the inflammation continues to smolder, leading eventually to chronic lung abcess. Another example of chronic inflammation with a persistent stimulus is peptic ulcer of the duodenum or stomach. The response may be chronic almost from the onset. Acute to chronic transition occurs when the acute inflammatory response cannot be resolved, owing either to the persistence of the injourious agent or to some interference in the normal process of healing. For example, bacterial infection of the lung may begin as a focus of acute inflammation (pneumonia), but its failure to resolve may lead to extensive tissue destruction and formation of a cavity in which the inflammation continues to smolder, leading eventually to chronic lung abcess. Another example of chronic inflammation with a persistent stimulus is peptic ulcer of the duodenum or stomach.

Factors that influence soft tissue inflammation and repair

- **Infection**
  It promotes further inflammation and tissue destruction

- **Age and nutritional status**
  Elderly people have a greater incidence of vascular disease
  Major deficiency of vitamin C and protein

- **Concurrent disease**
  1. Diabetes mellitus
     - Atherosclerosis and ischemia

- Incresed susceptibility to microbial infections (diminished chemotaxis and impaired phagocitic function of neutrophils)

2. Vascular diseases
   - Reduced blood supply
3. Uremia
   - Diminished chemotaxis
   - Decreased circulatingg lymphocytes
   - Suppresion of delayed hypersensitivity
4. Blood diseases and white cell dysfunction
   - Hemorrhagic diseases: excessive bleeding into sites of infection
   - Leukemia, lymphoma, myeloma: decreased number of effective phagocitic white cells→ opportunistic infections

➢ **Immunosuppressive drugs**

Glucocorticoid drugs inhibition of inflammation and repair:
- Prevent attachement of white blood cells
- Inhibit vascular permebility
- Inhibit leukocyte migration
- Inhibit release of enzyme from lysosomes

➢ **Foreign bodies**
- Dacron (for replacement of bones, joints, major vessels, and heart valves)

Disorders of leukocytes

I. DEFECTIVE PRODUCTION (NEUTROPENIA)

1. Drug induced neutropenia
2. Associated with aplastic anemia
3. Associated with acute leukemia
4. Associated with splenomegalia
5. Idiopathic neutropenia

II. DEFECTS OF LEUKOCYTES FUNCTION

1. Defects of adhesion

➢ Leukocyte adhesion deficiency

Autosomal recessive disorder
- Deficiency in the biosynthesis of the B chain of the leukocyte integrins (LFA-1, Mac-1)

2. Defects of chemotaxis
- Intrinsic cellular defects:
  a. Abnormal deformability (eg. Chédiak-Higashi sdr.)

  b. Abnormal random migration ("lazy leukocyte" sdr. – defective polymerisation of actin in the microfilamments)
  c. Abnormal directed migration in response to chemotaxins
- Extrinsic cellular defects: defective generation of chemotactic factors
  a. decreased production (eg. deficient complement components C3, C5)
  b. Inhibition of chemotactic factor formation and action (eg. uremia, cirrhosis)
  c. Circulating chemotactic factor inactivator (Hodgkin's disease)

3. Defects of phagocitosis
- Intrinsic cellular defects: neutrophil "actin dysfunction" ; diabetes mellitus
- Extrinsic cellular defects: deficiency of immunoglobulins or complement →failure of leukocytes opsonisation

4. Defects of bactericidal activity

Chronic granulomatous disease
- Genetic abnormality
- Deficiency of NADPH oxidase
- Neutrophils are defenseless against bacteria (eg. Staphiloccocus aureus) which inactivates hydrogen peroxide

5. Mixed defects

Chédiak-Higashi sdr.
- Autosomal recessive disorder
- Neutropenia
- Decreased chemotaxis (disordered assembly of microtubules)
- Defective degranulation
- Delayed microbial killing
- Neutrophils have giant granules

Diabetes mellitus

Impaired motility

I.6. PATHOPHYSIOLOGY OF PROTEIN METABOLISM

The nitrogenous compounds of blood plasma encompass all those organic and inorganic nitrogen- containing compounds of blood. These include the organic macromolecular compounds such as the proteins and nucleic acids: the smaller molecular weight compunds such as glutathione, urea and creatinine and the inorganic compunds such as nitrate and ammonia. The nonpretein nitrogen compounds(NPN) compounds are those grouped together as the fraction of the N-containing compounds of protein that are not removed by the common precipitating agents such as trichloracetic. The principal components of the NPN fraction are urea

(50%) and amino acids (25%), which total about 35,7 mmol N/ liter plasma (50 mg N/dL) in contrast to protein nitrogen, which totals more than 714 mmol N/ liter (1g N/dL or 6,50 g protein /dL plasma). This chapter deals primarily with this latter fraction, which is classed collectivelly as the plasma serum proteins and with end products of protein metabolism.

Proteins are composed of aminoacids. There are 20 aminoacids present in body proteins in significant quantities, 9 of which are essentials to the body. These are leucine, isoleucine, methionine, phenilalanine, treonine, tryptophan, valine, lysine and histidine. The foods that provide these essential aminoacids are reffered to as complete proteins (milk, eggs, fish and poultry). The incomplete proteins are those that do not provide all nine essential aminoacids; these need to be combined with each other or with complete proteins to meet the aminoacid requirements.

Each gram of protein yields 4 calories. Because fatty acids cannot be converted to glucose, the body must break down proteins and use the aminoacids as a major source of substrate for ghaconeogenesis during periods when metabolic nedds exceed food intake. Diet that are inadequate in protein will result in protein kwashiokor. If both calories and protein are inadequate, protein- calorie malnutrition occur.

Unlike carbohydrates and fats, which are composed of hydrogen, carbon and oxygen, proteins contain 16% nitrogen; therefore, nitrogen excretion is an indicator of protein intake. If the amount of nitrogen taken in way of protein is equivalent to the nitrogen excreted, the person is said to be in nitrogen balance. An individual is in positive nitrogen balance when the nitrogen consumed by way of protein is grater than the amount excreted. This must occur during growth, pregnancy or healing after surgery or injuries, when protein intake must exceed 2,2 grams / kg body weight. A negative nitrogen balance often occurs during fever, illness, infections, trauma, burns when more nitrogen is excreted as nonprotein end products than is consumed (due to hypercatabolism).

Classification of proteins

1. Structural classification

Proteins are most frequently classified according to their form and composition:

- Primary structure: the aminoacid structure of a single polypeptide chain
- Secondary structure: the helical structure of the chain (α- helix)
- Tertiary structure: the folding of the helices into different shapes- ie, globular (myoglobin), linear (fibrinogen), etc. These are monomers.
- Quaternary structure: the combination of two or more monomers- ie, dimers (creatinkinase), tetramers (hemoglobin), etc.

2. Chemical classification

Proteins are also classed according to their chemical composition:

- Simple proteins contain the basic elements of the aminoacids: carbon, hydrogen, oxygen, nitrogen, sulfur.
- Conjugated proteins are those bound to elements, prostetic groups or to the other compounds:
  - metaloproteins – ferritin (iron)
  - phosphoproteins- casein (phosphate)
  - lipoproteins- both low and high density lipoproteins (free cholesterol, cholesterol esters, triglycerides, apoproteins)
  - glycoproteins- glicated hemoglobin, fructosamine
  - nucleoproteins- ribosomal proteins

3. Physical classification

Proteins have also been classified by their physical behavior: water and salt solubility, density, molecular weight and migration through an electrical curent.

The electrophoretic technique is the current standard of reference for the fractionation of the serum proteins. The principal of the electrophoretic separation of serum proteins is based on the migration of charged protein particles in an electrical field. The direction and rate of migration of the particles is based on the type of charge (most serum proteins are negativelly charged and they migrate toward the anode) and size of the protein, intensity of the electric field and the support medium through which the protein particles are induced to migrate.

Electrophoretogram shows the following protein fractions:

- Albumin, with the strongest negativity migrates farthest toward the anode.
- Globulins, with weaker negativities, migrate more slowly toward the anode. The globulins move in groups classed as the α1-, α2-, β- and γ- globulins.

Metabolism of proteins

The intake of nitrogen compounds and the maintainance of nitrogen balance essentially evolve about the intake and metabolism of the aminoacids of the ingested proteins. In the adult, excretory losses are balanced by intake so that a nitrogen equilibrium is maintained.

The fundamental units of protein structure are the 20 aminoacids. The essential aminoacids of this group are those not synthesized and hence must be supplied in the diet. The nonessential aminoacids are those that are synthesized through transamination reactions under the control of transaminases, enzymes widly used in clinical biochemistry as an index of liver function.

The major site of synthesis of plasma proteins is the liver. The second major site is the immune system, consisting of the monocyte- macrophage system, lymphoid and plasma cells. Structural, functional and enzyme proteins that are synthesized in all body cells and tissues are present in plasma in minor quantities as a result of cell tournover. In general, plasma contains about 65- 85 grams proteins / liter.

Tissue and plasma proteins are constantly being degraded to their constituent aminoacids and the aminoacids in turn are source of energy as well as sources of carbohydrate and fat carbon. The rate of degradation of the plasma proteins is expressed as their turnover, fractional clearance or as their half- time. Clearance half-time may range from a few hours (some enzyme proteins) to as long as 120 days for hemoglobin. The clearance half- time of most plasma proteins range between 1 to 3 weeks.

Both diet and tissue proteins are degraded to ammonia, as the end product of protein metabolism. About 75% of the ammonia is transported to the hepatocytes into the mitochondria and is transformed into urea through a cyclical process, called urea cycle. Urea excretion by glomerular filtration and tubular secretion are the major routes of nitrogen excretion. Disposal of ammonia by the kidney tubules is a second important route of nitrogen excretion. In the tubules, glutamine is deaminated to glutamate and ammonia by glutaminase. Ammonia in the tubular lumen is converted to ammonium by binding to hydrogen ion and is therefore an equally important mechanism for removal of excess hidrogen ions for the maintainance of acid- base balance.

There are many factors influencing the plasma proteins. At birth, plasma proteins are quite low due to the minimal quantities of immunoglobulins and low albumin, especially for premature infants. This is a result of insufficient liver synthesis. Some hormons (testosteron, estrogens, growth hormon) effect an increase in total plasma proteins due to their anabolic effects, whereas others (thyroxine, cortisol) tend to decrease the total plasma protein due to their catabolic effect.

The **functions** of plasma proteins in the body are innumerable. The biological activities of proteins and polypeptides for these various functions depend on their structure, from the primary aminoacid sequence of the polypeptide hormones to the macromolecular fibers of the fibrin polymers that participate to clot formation.

- They form the basis of structure of cells, organs and tissues. The amount of plasma proteins mirrors the profficiency of protein metabolism: hypoproteinemia causes the raise of muscular protein metabolism, thus resulting in muscular atrophy.
- The principal role of albumin is to provide coloid osmotic pressure and thus blood pressure. It is the most osmotically active plasma protein due to its abundance and small size and accounts for about 75% of the osmotic activity of plasma. Hypoproteinemia results in plasma loss from the capillaries and edema formation.

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- They are transport and carrier compounds for most of drugs and plasma constituents. For example, albumine has ability to bind various ligands: calcium, bilirubin, free fatty acids, certain steroid hormons and drugs such as aspirin, penicilin and other antibiotics. This function has important farmacological implications because of their involvement in drug farmakinetics. Virtually all constituents of plasma not bound and transported by a specific transport protein and even many that are (thyroxine) are transported by albumin. Albumin binding permits the effective transport of these substances in the aqueous plasma. Binding to albumin also prevents the loss of plasma chemical constituents through the kidneys. The binding of unconjugated bilirubin or of free fatty acids by albumin is an example of this function.
- They are buffers to maintain acid- base balance.
- They function in blood coagulation.
- They are regulators of many body function because of their hormonal (endocrine) action .
- Globulins are principally responsible for both the natural and the aquired immunity

The involvement of proteins as *the third carrier system of the body* is argued by some examples:

- A severe jaundice may be seen in premature infants in the first week of extrauterine life and it is related to the immaturity of the infant liver to synthesis the normal levels of albumin as a bilirubin carrier and to remove and conjugate sufficient amount of bilirubin. Kernicterus is a condition characterized by severe neurologic symptoms that are due to high blood levels of unconjugated bilirubin; because the unconjugated bilirubin is lipid-soluble, it is able to enter nerve cells and cause brain damage. It is more frequent in premature infants with incompatibility in Rh system and severe hemolysis; more than that, increased permeability of the blood- brain barrier in the premature neonates raises the risk of brain damages.
- Pregnancy and viral hepatitis are associated with high levels of thyroid hormons without signs of hyperthyroidism because of simultaneously hypersecretion of thyroxin- binding globulin.

Normal serum proteins

More than 200 plasma proteins (table 1) have been described and quantitated in man and animals. Many of these plasma proteins change markedly in disease and many change only subtley or not at all.

1. **Prealbumin** is the most rapidly migrating fraction in human serum. The only known function of prealbumin is thyroxine binding and transport.
2. **Albumine** is the most prominent of the serum proteins in humans, in which albumin accounts for 60- 70% of the total. It is synthetized by the liver as are all plasma proteins except for the immunoglobulins and it is catabolized by all metabolically active tissues. Its synthesis is enhanced by hormons such as growth hormon and insuline; its catabolism is stimulated by cortisol. Albumine is a major storage reservoir of proteins and as well as being a transporter of its constituent aminoacids. A major metabolic function of albumin is its role as a general binding and transport protein.
3. **Globulins**

α- **globulin fraction** is the most rapidly migrating of all the globulins and it migrates as an α1 (fast) and an α2 (slow) fraction. Most of the globulins of this fraction are synthesized by the liver, except for the α1- fetoprotein, which is synthesized by fetal liver cells. Important proteins of this fraction are the α-lipoproteins (HDL), which migrate as α1, and the pre- β-lipoproteins (VLDL), which migrate in the α2 position. The β- lipoproteins (LDL), so named because it migrates in the β- region, also in the α2 region. These later two lipoproteins togather with α2- macroglobulin account for the increase in α2- globulins seen in the nephrotic syndrome. The α2- macroglobulin, haptoglobin, ceruloplasmin and amiloid A are diagnostically important acute phase proteins (table 2).

β- **globulins** consist of some complement fractions, hemopexin, transferrin, ferritin and C- reactive protein. Fibrinogen slightly trails the β in plasma electrophoresis and is another acute phase protein. In response to the antigenic stimulus of infectious agents or in plasma malignancies, immunoglobulins can rise in the β zone as well in the γ zones.

γ- **globulins** are identified and quantified using immunochemical techniques as immunoglobulins G, A, M, E and D. The immunoglobulins are glycoproteins whose basic structure is a monomer comprised of two heavy and two light chains linked by disulfide bridges. The structure of the heavy chain governs the class of immunoglobulin. Structural variations in the variable regions of heavy and light chains provide a basis for further suddivision into subtypes and subclasses. To date, four subclasses of IgG have been identified and two subclasses of IgA. IgG, IgD and IgE are monomers; IgA is a dimer and IgM is a pentamer. Most viral, bacterial and toxin antibodies are of the IgG type. IgD has been reported only in humans, where its function is unknown. IgE is involved in allergic and anaphylactic reactions. IgA is a dimer of two basic units joined by a secretory piece; it is found in the secretions of the respiratory, genitourinary and gastrointestinal tracts. IgM is a cyclic pentamer of five basic units that forms a high- molecular weight unit.

Table 1: Common serum proteins, their function and changes in disease

Protein	*Function*	*Change in disease*
Prealbumin	Thyroxine transport	Increased: nephrotic syndrom, Decreased: protein deficiency
Albumin	Coloid-osmotic pressure Plasma transport	Increased: dehydration Decreased: liver diseases neprotic syndrom inflammations blood loss
Thyroxin- binding- globulin	Thyroxine transport	Increased: pregnancy
α- Fetoprotein	Unknown Used as tumoral marker	Increased: pregnancy, hepatoma
α- Antitripsin and antichimotripsin	Antiproteases	Increased: acute inflammation Decreased: liver diseases, lung emphysema
α- Antithrombin III	Thrombin inhibitor	Increased: disseminated intravascular coagulation (DIC)
α- Acid- glycoprotein (orosomucoid)	unknown	Increased: acute inflammations Decreased: liver diseases, nephrotic syndrom
α- Lipoprotein (HDL)	Lipid transport	Increased: habitual alcohol intake Decreased: diabetes mellitus
Pre- β- lipoprotein	Lipid transport	Increased: nephrotic syndrom, diabetes, chronic alcohol intake Decreased: malnutrition
α- Macroglobulin	Insulin binding Protease inhibitor	Increased: acute inflam-mation, chronic active liver diseases
Ceruloplasmin	Copper transport	Increased: acute inflammation
Haptoglobin	Hemoglobin binding	Increased: acute inflammation
β- Lipoprotein (LDL)	Lipid transport	Increased: nephrotic syndrome, hypothyroidism,
Transferrin	Iron transport	Increased: iron- deficiency anemia, Decreased: iron storage disease (hemochromatosis), acute inflammation
Complement C3 and C4		Increased: acute inflammation
C- reactive protein	Activates the complement system Nonspecific opsonine	Increased : acute inflammation
Plasminogen	Proenzyme of plasmin, fibrinolysis	Increased: primary and secondary fibrinolysis
Fibrinogen	Fibrin precursor	Increased: acute inflammation Decreased: congenital afibrinogenemia, DIC, liver failure
Immunoglobulins: IgG	Major antibodies in response to infections	Increased: inflammations Decreased: immune deficiency diseases
IgA	Secretory antibodies in the fluids of the respiratory, digestive and genito- urinary tracts	Similar
IgE	Antibodies of allergy	Allergies, anaphylaxis
IgM	Cold agglutinine Anti Rh antibody	Chronic inflammatory diseases
IgD	Unknown	

Table 2: Markers of acute inflammatory diseases: acute phase proteins (APP)

Positive acute phase proteins
α1- globulins
α1- antitrypsin and α1- antichimotripsin
α1- acid glycoprotein (orosomucoid)
α2- globulins
α2- macroglobulin
ceruloplasmin
serum amyloid A
haptoglobin
β- globulins
fibrinogen
complement C3 and C4
C- reactive protein
Amyloid A
Negative acute phase proteins
Prealbumin
Transfferin
Albumin

A specific plasma cell subpopulation of defined genetic origin- a clone- produces a specific immunoglobulin. Uncontroled growth of a single B- cell clone (malignancy) results in the overproduction of a single chemical species of immunoglobulin, which appear as a sharp monoclonal spike of monoclonal gammopathy on an electrophoretogram. A group of clones, each of a different genetic origin, can also overproduce a heterogenous mix of immunoglobulins, which appears as a diffuse or broad hyperglobulinemic region on the electrophoretogram. This region is described as a polyclonal gammopathy.

The Bence- Jones proteins are light- chain units and their presence reflects the asynchronous synthesis of heavy chains so that excess light chain appear. When they appear in the urine, they are called Bence- Jones proteins. They are often found to accompany gammopathies, especially malignancies of plasma cells, such as multiple myeloma.

THE DISPROTEINEMIAS

The first approach and method of choice for the overall evaluation of protein status is the use of serum electrophoresis. The electrophoretogram and the absolute values of the individual fractions provide an excellent basis for the presumtive

diagnoses. The albumin: globulin ratio derived from serum electrophoresis is the basis for protein metabolism interpretation.

A classification of the electropforesis profile in conjunction with the A: G ratio provides for a systematic approach to the interpretation of protein discrasias.

Normal A: G ratio

1. Hyperproteinemia

Simple dehydration with water loss is essentially the only instance when a simple hyperproteinemia without changes in profile or A: G occurs. In this case, all protein fractions increase proportionately, including albumin, because only water has been removed from the system.

2. Hypoproteinemia

Overhydration through vigorous fluid therapy or excess water intake is a common cause of simple hypoproteinemia. This is a simple dilution of the system.In other instances, for example, after acute blood loss, interstitial fluid moves rapidly into the plasma compartment, thus diluting the system. Similarly, after acute plasma loss, whether internal or external, by exudation or extravasation, simple hypoproteinemia occurs because the water losses are rapidly replaced by movement of interstitial water into the plasma compartment.

Decreased A: G ratio- abnormal profile

1. Decreased albumin

Decreases in albumin are common forms of dysproteinemia. Fundamentally, the decreases can be attributed to either albumin loss or failure of albumin synthesis. Depending on the stage of the disease, it can be associated with either normoproteinemia or, in its advanced stage, hypoproteinemia.

Due to small and osmotic sensitivity to fluid movements, albumin is selectively lost in glomerulopathies (nephrotic syndrom), intestinal diseases (exudative enteropathies)and in intestinal parasitism.

Furthermore, due to the sensitivity of albumin synthesis to protein and nitrogen loss such as that occuring in any form of diarrhea, albumin loss impairs albumin synthesis and further compounds hypoalbuminemia. Due to the same sensitivity of albumin synthesis to protein and nitrogen availability, decreased albumin precedes the development of generalized hypoproteinemia in dietary protein deficiency. Classic human protein- calorie malnutrition called kwashiorkor is characterized by hypoalbuminemia and hypoproteinemia.

The liver is the only site of albumin synthesis and hypoalbuminemia is an important feature of chronic liver disease. Additionally, albumin is a negative acute phase protein and extensive inflammations are associtaed with hypoalbuminemia.

2. Increased globulins

α1- globulins but mainly α2- globulins increases are commonly found and are of diagnostic significance. Many APPs migrate in the α1- and α2- globulin region so that increases in these globulins are a common finding in acute inflammatory diseases. In the nephrotic syndrome, α2- globulins increase due in part to the α2-macroglobulin and the lipoproteins. The triad of azotemia, hypoalbuminemia and hypercholesterolemia is a characteristic of the nephrotic syndrome.

Increases of β- globulins alone are infrequent and found in association only with active liver diaseases and in the nephrotic syndrom. Transfferin appears to be the major component that rises in active liver disease togather with complement.

Increased γ- globulins: policlonal gammopathy (broad increase)

The diffuse or broad increases in the γ- globulins that characterize polyclonal gammopathies are the result of the heterogenity of the clones of plasma cells, which produce a heterogenous mix of immunoglobulins. Any one or all of the immunoglobulins IgM, IgG or IgA can be present, but a preponderence of one is usually seen.

The chronic inflammatory disease profile may be manifested by a variety of disease states such as chronic infections, collagen diseases and malignancies. There is a concomitant decrease in albumin as a result of decreased synthesis. Immunological mediated disease processes are also characterized by polyclonal increases. These may be immune processes directed against self- autoimmune disease, or against external antigenic stimuli.

Increased γ- globulin: monoclonal gammopathy (sharp increases)

The monoclonal forms are characterized by sharp spikes of immunoglobulin and are frequently limited to the γ- region. The monoclonal spike is the result of a single clone producing a single class of immunoglobulins, usually abnormal in nature. These immunoglobulins have been described as paraproteins or as the M components because of the frequent occurence of IgM. In multiple myeloma, light chains of immunoglobulins (Bence- Jones proteins) are detected. Tumors of the monocyte-macrophage system frequently present with monoclonal spikes depending on the degree of cloning of the tumor cells.

Increased A: G ratio- abnormal profile

1. Increased albumin

True overproduction of albumin does not occur in humans. Therefore, any rise in albumin is only a relative hyperalbuminemia due to hemoconcentration as a result of water loss and dehydration.

2. Decreased globulins

Hypo- γ- globulinemia occurs in immunodeficient syndroms, accomanied with lymphopenia.

3. Fibrinogen is a large protein which constitutes about 5% of the total proteins of the plasma. Hyperfibrinogenemia is a common characteristic of inflammatory processes.

Hypofibrinogenemia is a condition resulting from increased consumption in disseminated intravascular coagulation, increased destruction in primary fibrinolysis or decreased synthesis in liver failure.

PATHOGENESIS OF PROTEIN METABOLISM ABNORMALITIES

Protein deficiency is present when inssuficient energy or protein is available to meet metabolic demands. Inadequate dietary intake, increased metabolic demands due to diseases and increased nutrients losses are the most common mechanisms by which the body protein may become disrupted. Protein deficiency may also arise in the face of adequate protein intake if the dietary protein is of poor quality. Protein intake is also influenced by the intake oof energy relative to the intake of protein because the efficient utilization of dietary protein requires energy from nonprotein calories.

The most frequent causes of protein deficiency are included in table 3.

Table 3: Etiology of protein deficit

1. Deficit of protein intake, maldigestion, malabsorbtion
Anorexia nervosa
Poor people
Deficiency of digestive enzymes
Primary malabsorbtive states
2. Increased protein losses
Protein- losing enteropathy
Nephrotic syndrom
Enteric fistula
Burns
3. Decreased protein synthesis
Liver failure
Congenital states associated with specific absence of proteins
Congenital analbuminemia
Congenital afibrinogenemia
Congenital agammaglobulinemia

Adaptive responses function over a short term when protein and energy sources are limited. The mobilization of aminoacids form skeletal muscles is an adaptive response due to both increase of circulating catecholamins, glucagon, cortisol and hypermetabolism associated with severe illness. The liberated aminoacids are in part

used as fuels. They are also taken up by the liver and other visceral organs (the visceral protein compartment). The proteolysis of muscles enableas the body to shift protein substrate from skeletal muscle (the somatic protein compartment)to visceral organs whose function is more critical for survival.

The consequences of protein deficit are noted in table 4.

Table 4:Physiological impairements associated with protein- energy malnutrition

1. *Gastrointestinal tract:*
   - atrophy of the intestine
   - absence of the intestinal villi
   - decreased levels of the disaccharidases and aminopeptidases in the mucosa
   - decreased concentration of the digestive enzymes in the bile, gastric and pancreatic juice
   - secondary maldigestion and malabsorbtion
2. *Immunological functions:*
   - impairement of nonspecific defence mechanisms: atrophy of epithelial integrity, decreased of lysozyme secretion, decreased phagocytosis
   - impairement of both cellular and humoral immunity
   - complement system is blunted
3. *Endocrine function:*
   - inadequate food intake → decreased availability of circulating levels of insulin in conjunction with the decreased levels of somatomedins and increased levels of cortisol → increased protein catabolism in the skeletal muscles
   - serum levels of thyroid hormons are decreased, resembling the pattern observed in the euthyroid sick syndrom
   - gonadal disfunction: amenorrhea, reduced fertility, delay of puberty due to decreased of pituitary- gonadal axis
4. *Cardiovascular system*
   - structural changes of the myocardium: myofibrilar atrophy, edema, necrosis and infiltration with chronic inflammatory cells
   - involvement of the conduction system
   - alteration in myocardial performances: decreased cardiac output, reversible to nutritional repletion
5. *Respiratory system:*
   - atrophy of the respiratory muscles
   - ventilatory disfunctions
6. *Wound healing:* decreased collagen deposition at the site of surgical wound, delay woumd healing

The classic approach to the study of this situation in underdeveloped countries, commonly divides cases into **marasmus** and **kwashiorkor**.

Marasmus is characterized by progressive wasting due to indequate food intake that is equally deficient in calories and proteins. The child with marasmus has a

wasted appearance with stunted growth and loss of subcutaneous fat, but with relatively normal skin, hair, liver function and affect.

Kwashiorkor results from a protein deficiency . The term comes form african word meaning the disease suffered by the displaced child, because the condition develops soon after a child is displaced from the breast and placed on a starchy gruel feeding following the arrival of a new baby. The child with kwashiorkor has edema, desquamating skin, discolored hair, hepatomegaly, anorexia and extreme apathy.

Protein status can be assessed in several different ways. The accuracy of serum albumins to reflect the status of the visceral protein compartment is low: the long half- time of albumin (20 days), the fact that it is distributed extensivelly in the extravascular and intravascular compartments and the fact that its synthesis is influenced by circulating inflammatory mediators and by liver diseases. Other serum proteins with shorter half- lives such as transferrin, prealbumins and retinol- binding protein are better in this regard.

DISORDERS OF AMINOACIDS AND STORAGE

All polypeptides and proteins are polymers of 20 different amino acids. Eight of these, reffered to as essentials cannot be synthesized by human and must be obtained from dietary sources. The others are formed endogenously originating form cetoacids through transamination catalized by the enzymes called transaminases.

Table 5: Classification of aminoacid disorders

- Hereditary aminoaciduria
  - Associated with decreased renal tubular reabsorbtion
    - Cystinuria
    - Cystinosis
    - Fanconi syndrom
    - Hartnup disease
  - Without decreased renal tubular function
    - Hyperphenylalaninemias
- Acquired aminoaciduria
  - Associated with decreased renal tubular reabsorbtion
    - Nephrotic syndrom
    - Acute tubular necrosis
    - Nephrotoxins
  - Without decreased renal tubular function
    - Liver failure
    - Starvation

Physiologically, aminoacids are "building blocks". Some of them (glutamat, gama- aminobutiric acid) are neurotransmitters. Others are precursors of hormons, coenzymes, pigments, purines and pyrimidines.

The disorders of aminoacids are named for the compound that accumulates to hight concentration in blood (- *emias)* or urine (- *urias).* For many conditions (often called aminoacidopathies), the parent aminoacid is found in excess; for the others, products in the catabolic pathway accumulate. Which compound accumulates depends on the site of enzymatic block, the reversibility of the reactions proximal to the lesion and the availability of the alternative pathways.

Cystinuria

It is the most common inborn error of aminoacid transport, characterized by impaired tubular reabsorbtion and excessive urinary excretion of the dibasic acids lysine, arginine, ornithine and cystine. A similar transport defect exists in the intestinal mucosa. The basic defect is the alteration in the membrane carrier protein essential for the transport of this group of aminoacids in the apical brush border of proximal renal tubule and small intestinal cells.

Because cystine is the least soluble of the naturally occuring aminoacids, its oevrexcretion predsipose to the formation of renal, ureteral and bladder stones.Reccurent urolithiasis may lead to progressive renal failure.

Cystinosis

It is a rare disorder characterized by the intralysosomal accumulation of free cystine in body tissues. This results in the appearance of cystine crystals in the cornea, conjunctiva, bone marrow, lymph nodes, leukocytes and internal organs. The basic defect involves impaired efflux from lysosome which is an active ATP-dependent process. Cystine accumulation in the kidneys causes renal insuficiency and generalized proximal tubular disfunction (Fanconi syndrom) with hyperphosphaturia, hypophosphaturia, renal glucosuria, generalized aminoaciduria, hypouricemia, hypokalemia. Growth retardation, vomiting, fevr, vitamin D- resistant rickets, polyuria, dehydration and metabolic acidosis are prominent.

Hartnup disease

In this rare disease, renal and intestinal transport of monoanino- monocarboxylic aminoacids (ie, thryptophan) is defective. Dietary aminoacids undergo bacterial degradation in the intestinal lumen. At the time they are lost in the urine. Inadequate thryptophan availability limits nicotinamide synthesis and leads to secondary pellagra: an erythematous rash appear after exposure to sunlight and episodic cerebellar ataxia emotional instability and delirium occur.

Most patients respond to treatment with oral nicotinamine and a high protein diet to compensate for aminoacid malabsorbtion and loss.

Fanconi syndrom

It is a constellation of transport defects in the proximal tubule involving aminoacids, monosaccharides, sodium, potasium, calcium, phosphate, bicarbonate, uric acid and proteins. Generalized aminoaciduria, glucosuria, salt wasting, hypercalciuria, hypophosphatemia, proximal renal tubular acidosis due to bicarbonate loss, hypouricemia and tubular proteinuria may result. Fanconi syndrom may be secondary to diseases such as cystinosis.

Typically, there is a cellular atrophy of the initial portion of the proximal tubule which is probably the anatomic basis of this tubular disorder.

Dwarfism and hypophosphatemic rickets occur along with the laboratory abnormalities of Fanconi syndrom.

Hyperphenilalaninemias

They result from impaired conversion of phenylalanine to tyrosine. The most common and clinical important is phenilketonuria, which is characterized by an increased concentration of phenylalanine in the blood, increased concentration of phenylalanine and its end- products (notably phenylpyruvat, phenylacetat, phenillactateand phenylacetylglutamine) in the urine and severe mental retardation.Each of forms results from reduced activity of phenylalanine hydroxylase. Phenylalanine accumulation in the blood and urine and reduced tyrosine formation are direct consequences of the impaired hydroxylation. Plasma concentration of phenylalanine becomes sufficiently high to activate alternative pathways of metabolism and lead to formation of other derivates that are rapidly cleared by the kidneys and excreted in the urine (pnenylketonuria)/

The severe brain damages are due to several consequences of phenylalanine accumulation: competitive inhibition of transport of other aminoacids for protein synthesis, impaired polyribosome formation and stabilisation, reduced myelin synthesis and inadequate formation of norepinephrine and serotonin. Phenylalanine is a competitive inhibitor of tyrosinase, a key enzyme in the pathway of melanin synthesis. This block, plus reduced availability of the melanin precursor tyrosine, accounts for the hipopigmentation of hair and skin.

PROTEIN METABOLISM END PRODUCTS

Urea

Proteins, as the major dietary source of nitrogen, are hydrolyzed in the intestine to their constituent aminoacids and absorbed by the intestinal mucosal cells. Intestinal bacteria may also degrade the aminoacids so that ammonia itself may be absorbed.

About 75% of the aminoacids and ammonia are transported across the liver cell membrane to be taken up by the liver cell and on into the mitochondria. In the mitochondria, ammonium ion, bicarbonate and ornithine form citrulline which moves to the cytoplasma where forms urea.

Thus, urea is the major disposal form of amino groups derived from the catabolism of aminoacids. It is synthesised in the liver and then enter the blood and is excreted in urine.

Normal range in the plasma (20- 40 mg/dL) reflects the balance between urea formation and elimination. Normal level in the plasma exceeds the blood concentration because red blood cells do not contain urea. Blood urea, also called *blood urea nitrogen (BUN)* is 9-20 mg/ dL.

Increased urea level :

- increased protein catabolism: fever, inflammations, hyperthyroidism, cancers, diabetic ketoacidosis
- increased dietary proteins
- oligoanuric stage of chronic renal failure or other renal abnormalities accompanied by decreased glomerular filtration rate and tubular function
- digestive hemorrhages which lead to hypovolemia and secondary to decreased renal perfusion and prerenal azotemia

Decreased urea level:

- decreased liver synthesis of urea in advanced liver failure
- poliuric phase of renal failure
- pregnancy
- anabolic states due to androgen therapy

Creatinine

It is formed at a constant rate as a end product of creatine and phosphocreatine metabolism in the muscle. The amount of creatinine excreted by the body is proportional to the muscle metabolism which reflects the total content of creatine phosphate in the body, and thus can be used to estimate the muscle mass and metabolism.

Creatinine level in the plasma reflect the balance between the synthesis and excretion. The synthesis is considered proportional to muscle mass and metabolism and is at a constant level. It is removed from the body by glomerular filtration, thus creatinine is a more sensitive marker of renal function, especially of glomerular filtration, that urea.

When muscle mass and active muscle metabolism decrease for any reasons (muscle paralyses, muscle distrophies, polymyositis) the creatinine content of the plasma and urine falls but creatine and creatinphosphokinase are lost in the urine.

Renal failure and glomerulonephritis are accompanied by high levels of plasma creatinine.

Uric acid. Pathophysiology of gout

Gout is the common end point of a disorders that produce hyperuricemia. It is marked by transient attacks of acute arthritis initiated by crystallization of urates within and about joints, leading eventually to chronic guoty arthritis and the deposition of masses of urates in joint and other sites creating tophi. Most but not all patients with chronic guot also develop urate nephropathy. Althuogh hyperuricemia is a sine qua non for the development of gout, is not the sole determinant as the following data indicate. More than 10% of the population have hyperuricemia, but gout develops in fewer than 0.5% of the population. A plasma urate level above 7 mg/dl is considered elevated because it exceeds the saturatin value for urate at normal body temperature and blood pH.

The various conditions producing hyperuricemia and gout are shown in table 6, which divided them into "primary gout", in which the basic metabolic defect is unknown or gout is the main manifestation of known defect, and "secondary guot", in which the cause of the hyperuricemia is known or gout is not the main clinical dysfunction.

Tabel 6. Classification of gout

Clinical category	Metabolic effect
Primary gout (90%)	
Enzyme defects unknown (85-90% of primary gout)	Overproduction of uric acid Normal excretion (majority) Increased excretion (minority) Underexcretion of uric acid with normal production Overproduction of uric acid
Known enzyme defects- e.g. partial HGPRT deficiency (rare)	
Secondary gout (10% of cases)	Overproduction of uric acid with increased urinary excretion
Associated with increased nucleic acid turnover – e.g. leukemias	Reduced excretion of uric acid with normal production
Chronic renal disease	Overproduction of uric acid with increased urinary excretion (Lesh-Nyhan syndrome)
Inborn errors of metabolism – e.g. complete HGPRT deficiency	

HGPRT = hypoxantine guanine phosphoribosyl transferase

Uric acid is the end product of purine metabolism. Two pathways are involved in purine synthesis:

1. a "de novo" pathway, in which purines are synthesized from nonpurine precursors
2. a "salvage" pathway, in which free purine bases derived from the breakdown of nucleic acids of endogenous or exogenous origin are recaptured (salvaged). Hypoxantine guanine phosphoribosil transferase (HGPRT) is involved in the salvage pathway. A deficiency of the enzymes leads to increase synthesis of purine nucleotides through the de novo pathway and hence invreased production of uric acid. A complete lack of HGPRT occurs in the un common X-linked Lesch-Nyhan syndrome, seen only in males and charcterized by hyperuricemia, severe neurologic deficits with mental retardation and self-mutilation, and in some cases gouty arthritis. Less severe deficiencies of the enzymes may also induce hyeruricemia and gouty arthritis with only mild neurologic deficits, but together these causes of gout are uncommon. The great majority of cases of gout are "primary", in hich, frustratingly, the metabolic defect underlying the incraese levels of uric acid is unknown.

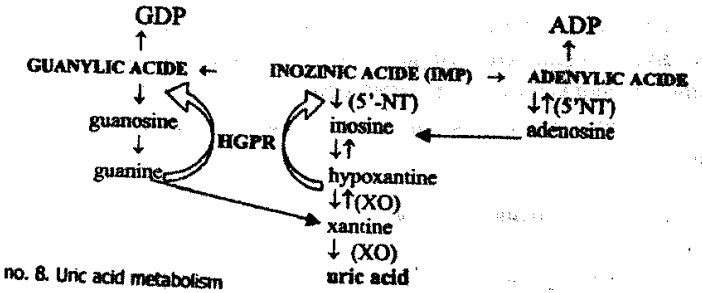


Figure no. 8. Uric acid metabolism

Pathogenesis of gout

Many factors play a role in the conversion of asymptomatic hyperuricemia into primary gout. Some of these are:

- Age of individual and duration of the hyperuricemia – gout rarely appears before 20 – 30 yares of hyperuricemia
- Genetic predisposition – in addition to the well deffined K-linked abnormalities of HGPRT, primary gout follows multifactorial inheritance and terefore runs in families
- Heavy alcohol consumption predisposes
- Obesity predisposes

- Certain drugs predispose – e.g., thiazide
- Lead toxicity predisposes to saturninee gout

Central to the pathogenesis of the arthritis is precipitation of monosodiun urate (MSU) crystals into the joints. Synovial fluid is a poorer solvent for MSU than plasma, and so in hyperuricemia the urates in the joint fluid become supersaturated, particularly in the peripheral joints, which may have temperatures as low as 20° C in the ankle. With prolonged hyperuricemia, microtophi of urates develop in the synovial lininig cells and in the joint cartilage. Some unknown event, possibly trauma, then initiates release of crystal into the synovial fluid followed by a cascade of events. The released crystals are chemotactic and also activate complement, with the generation of C3a and C5a, leading to the accumulation of neutrophils and macrophages in the joints and synovial membranes. Phagocytosis of crystals induces release of toxic free radicals and leukotriens (LTB4). Death of the neutropils releases destructive lysosomal enzymes, and the macrophages and synoviocytes secrete a variety of mediators, including IL-1, Il-6 and IL-8, and TNF- which further intensify the inflammatory reaction and augment the injury to the articular structures. Thus comes about an acute arthritis, which typically remits (days to weeks) even untreated.

Repetead attacks of acute arthritis lead eventually to chronic arthritis and th formation of tophi in the inflamed synovial membranes and particular tissues as well as elsewhere. In time, severe damage to the cartilage and the function of the joints develops. It is not known why the chronic arthritis is asymtomatic for intervals od days to months even though synovial crystals are undoubtedly present in abundance in the joints.

I.7. PATHOPHYSIOLOGY OF LIPID METABOLISM

The major lipids in blood plasma include:

1. free fatty acids (FFA)
2. triglycerides (TG)
3. phospholipids (PHi)
4. cholesterol (Chol)

1. **Fatty acids** are obtained from dietary sources by hydrolize of TG, by biosynthesis from intermediate molecule derived from the catabolism of sugars and certain amino-acids.

2. **TG** are formed by glycerol and three molecules of fatty acids.

They may be hydrolized by two enzymes to form fatty acids:

- lipoprotein-lipase, secreted by the endothelial cells and activated by heparin;

• adipose-lipase , activated by the hormons such as cortison or adrenalin.

3. **Phospholipids** are formed by glycerol, two molecules of fatty acids, a molecule of phosphoric acid and a molecule of choline.

4. **Cholesterol**. Cells require cholesterol for normal function and they obtain it from two major sources:

• biosynthesis from acetyl-CoA using some enymes. One of them is HMG-CoA reductase. Her activity may be decreased when the cells contain high level of cholesterol.

• uptake of chol from the intestinal fluid.

Depending on the tissue, the cholesterol can be used for new memebrane formation, bile acid formation (liver), estrogen production (ovary), testosteron production (testis) or mineralocorticoid and glucorticoid production (adrenal gland).

Role of lipoproteins (LP) and lipid transport.

Lipids are insoluble in the plasma. They exist there associated with proteins in macromolecular complexes caled lipoproteins.

Lipoproteins are spherical particles that contain:

- polar components: phospholipids
  unesterified cholesterol
  apoproteins

on the surface in contact with body fluids

- a core of nonpolar lipid, including cholesteryl esters (chol. combined with a fatty acid) and triglyceride. The proteins of LP are called apoproteins (Apo); they are required for several important metabolic functions such as:

  - the synthesis of LP;
  - the activation of enzymes important in lipoprotein metabolism
  - the interaction of lipoproteins with cell surface receptors that promote the cellular uptake of LP.

The plasma LP are divided into five major families. The families are differentiated from one another by certain physical and chemical properties, such as their hydrated density range or their migration during electrophoresis. Density range divides LP into the following families:

1. chylomicrons (Ch)
2. VLDL
3. IDL
4. LDL
5. HDL

The density of a LP is determined largely by the **ratio of protein to lipid** in the **particle.**

The least-dense lipoproteins contain the least amount of protein as a percent of their composition. As the protein content in a lipoprotein family increases relative to lipid, the hydrated density also increases.

The least dense LP are also the largest and contain the greates amount of tryglyceride: ex. chylomicrons and VLDL. In contrast, HDL particles, the most dense of the lypoproteins, are the smallest in size and contain more phospholypid per particle than the lypoproteins of lower density.

The exogenous paths of lipid transport

1. Chylomicrons are synthesized in intestinal epitelial cells in response to the ingestion of dietary fat. The fatty acids are esterified to tryglycerides, which then combine with cholesterol, Apo B-48, A I, A II, for secretion into the lymph as Ch. The Ch. traverse the lymphatics to enter the plasma via the thoracic lymph duct. In the plasma they acquire C I, C II, C III and E by simple exchange, primarily from HDL. As Ch. enter capillaries, they attach to lipoprotein lipase anchored to capillary endothelial cells. Lipoprotein lipase is activated by Apo C II to hydrolise the core triglyceride to from fatty acids, which are taken into tissues for oxidation or storage for future use (adipous tissue).

After most of the chylomicrons - triglyceride core is hydrolized, the particle dissociates from lipoprotein-lipase as Ch.-s remnants. These reamnants are depleted of TG and Apo-C peptides but they retain Apo-B 48, Apo E and the cholesterol. Originally, the remnant particles are rapidly removed from the circulation in the liver by a chylomicron remnant receptor that binds with Apo E.

Ch. enter the plasma whenever a meal contailung fat is consumed and they are removed from the plasma with a half-life of about 30 minutes.

The endogenous pathway or lipid tranasport

2. VLDL are somewhat smaller in size and of higher density than the chylomicrons. They are produced in the liver by converting carbohydrate to fatty acids, esterification of fatty acids with glycerol to endogenous triglycerides and secreted as TG lich particles containing Apo 13 100, Apo E and the Apo C peptides. VLDLs also acquire Apo C and Apo E by transfer from HDL. VLDL interact with lipoprotein-lipase in capillaries where the TG core is hydrolised to yield FFA principally for adipous tissue and muscle.

3. When VLDL remnants are released by lipoprotein-lipase they are termed intermediate density lipoproteins (DDL).

A portion of the LDL particles is catabolized by the liver through binding to receptors called low-density lipoprotein (LDL) receptor which arc distinct from the chylomicron remnant receptors.

The remaining IDL in plasma undergo a further transformation in which nearly all the residual TG are removed, all the apoproteins are removed except Apo B 100. The result is the transformation of the LDL particle into cholesterol-rich LDL.

4. Low-density lipoprotein (LDL): the core of LDL is composed entirely of cholesteryl-esters and surface coat contains only one apoprotein: Apo B loo.

The metabolism LDL involves two pathways:

a. Specific pathway

One function of LDL is to supply cholesterol to a variety of extrahepatic parenchymal cells such as adrenal cortical cells, lymphocytes and renal cells. These cells have LDL receptors on their membrane. Cells will take up chol. from the plasma in the form of LDL via the LDL receptor. The interaction of LDL with its receptor is mediated by Apo B 100. Tile receptor-lp complex is internalized in endosomes. The LDL is disassociated from the receptor meanwhile the LDL undergoes intracellular digestion in liposomes to liberate the cholesteryl esters. These esters are then hydrolized in lysosomes to yield free ch. for cellular use.

When adequate amounts of chol. are entering the cell via the LDL receptor pathway, cells supress the endogenous synthesis as reflected by the decreased activity of HHG-CoA reductase, the rate limiting enable in chol. biosynthesis. Cells also decrease the number of LDL receptors and they increase the activity of acyl-CoA-cholesterol acyl-transferase to esterify any excess cholesterol for storage as cholesteryl ester droplets.

b. Non-specific pathway. Much of the remainder cholesterol LDL is degraded by a scavenger cell system in phagocytic cells in the reticulo-endothelial system. This system functions solely to degrade LDL when the lypopretein reaches high concentrations in plasma rather than to supply cholesterol to cells. Thus macrophages engulph LDL-cholesterol to become foam cells. They are important structures of atherosclerotic plaque.

5. HDLs contain 50% proteins, especially Apo A and 50% lipids. It appears that the tissues produce nascent HDL particles containing Apo A I phospholipids and unesterified cholesterol. This nascent HDL acquires additional cholesterol by simple exchange when they come in contact with cell membranes. The efficiency of HDL as a cholesterol transporter from the tissues to the liver is enhanced by the activity of lecithin cholesterol acyltransferase (LCAT). LCAT esterifies the chol on the surface of the nascent HDLs. This reaction is facilitated by Apo A I. cofactor for LCAT.

HDL exchange lipids with other LP through the action of cholesteryl ester transfer protein (CETP). CEPT transfers cholesteryl esters from HDLs to Ch., VLDL and IDL. If this transfer is to Ch. remnants the transfered cholesteryl esters are returned to the liver. Some of the cholesterol that reaches the liver is converted to bile acids which are excreted into the intestine to act as detergents and facilitate the absorption of dietary fats. In addition, some cholesterol is excreted with the bile

without metabolism to bile acids. This process is called reverse cholesterol transport". This HDL is considered an antiatherogenic LP.

Disorders of lipid metabolism

Disorders of lp metabolism are associated with a variety of clinical features. The term hyperlipidemia is applied when the plasma or TG levels are increased.

LP disorders can be primary or secondary to some other disease process.

The primary LP disorders:

They are classified by Frederikson into five types:

Type I	Familial hyperchylomicron emia	Elevated chylomicrons Elevated triglyceride (TG) Normal cholesterol (chol)	Familial lipoprotein-lipase deciciency Familial apoprotein C II decficiency Decreased catabolism of TG
Type IIa	Familial hyper-cholesterolemia	Elevated LDL Elevated chol. Normal TG	Deficiency of LDL receptor and IDL catabolism is blocked
Type IIb	Familial combined hyperlipemia	Elevated LDL and VLDL Elevated chol and TG	Overproduction of VLDL by the liver
Type III	Familial dysbetali-poproteinemia	Elevated IDL and chylomicron remnants	Decreased uptake of IDL and chylomicron-remnants by the liver because of abnormal apoprotein E of VLDL (genotype E^2/E^2)
Type IV	Endogenous hyper-triglyceridemia	Elevated VLDL Elevated TG	Excessive carbohydrate intake Overproduction of VLDL or underlying defect in the ability to catabolize the TG of VLDL
Type V	Mixed hyper-triglyceridemia	Elevated chylomicrons and VLDL TG greatly increased	unkown

Type I is characterized by the massive accumulation of Ch in the plasma. Etiology and pathogenesis: this disorder is caused by two categories of causes:

- familial lipoprotein lipase deficiency
- familial Apo C 11 deficiency.

Consequently, when patients ingest fats and generate ch, they are unable to catabolize the ch and develop massive hyper ch-emia. Since the hyperlipidemia is generated from dietary fat, these patients have exogenous hyperlipidemia

Clinical manifestations; hepatosplenomegaly (macrophages may ingest Ch to produce foam cells) recurrent attacks of abdominal pain associated with the severe hyperTG, lipemia retinalis, which gives the white or pale appearance to the retinal vessels is due to the turbid plasma; premature atherosclerosis is not a feature of this disease.

Diagnosis:

1. Opalescent plasma after 8 to 12 hour fast

The Ch layer is especially evident following overnight refrigeration of the plasma.

2. TG levels may be reached, depending on the degree of dietary fat consumption.

3. Lipoprotein electrophoresis will demonstrate the increased level of ch, showing a type I patter.

Special centers will provide LPL assays following intravenous heparin injection - the so-called post-heparin lipolytic activity of lipoproteinlipase. The heparin releases lipoprotein-lipase from its capillary binding sites into the plasma where it can be assayed. Treatment: lifelong restriction of dietary fat is required to control the hyper TG.

Type II is divided into two subtypes:

II a: Familial hyperCol is characterized by increased risk for the development of premature atheroselerosis.

Etiology and pathogenesis:

In familial hyper Col, the gene for the LDL receptor is defective. Consequently, the LDL chol level rises in the blood and leads to accelarated deposition of chol in the artery wall. The coronary arteries are most commonly involved.

Clinical features:

- tendon xantomas in various locations, including the Achilles tendon.
- xanthelasmas
- symptoms of coronary heart disease: chest pain, myocardial infarction

Diagnosis:

- the plasma is clear, not lactescent
- biochemical tests show hyperchol
- lipoprotein electrophoresis demonstrates the increased level of LDL.

II b. Type II b pattern is associated with the increased level of LDL+ VLDL.

It is thought to be a part of familial combined hyperlipidemia. Affected individuals in a single family characteristically show one of three different lipoprotein patterns:

- hypercholesterolemia (type II a)
- hypertrygyceridemia (type IV)
- hyperchol and hyper TG (type II b).

The disease is transmitted as an autosomal dominant trait, implying a mutation in a single gene.

Clinical manifestations:

This disease is also associated with premature atherosclerosis and premature heart disease.

Diagnosis:

- the plasma is opalescent
- hyperchol, hyperTG or both lipid abnormalities
- lipoprotein electrophoresis: the incresed level of LDL or / and VLDL.

Some affected individuals may have all elevated rate of secretion of VLDL by the liver. Depending on the interplay of factors governing the efficiency of conversion of VLDL to LDL and the efficiency of catabolism of LDL, the overproduction of VLDL may manifest itself alternatively as an elevation in plasmaVLDL level, an elevation in LDL level or both.

Familial type III hyperlipoproteinemia

In this type, remnants of VLDL and ch metabolism accumulate to produce hyperlipidemia. The disorder is also referred to as primary dysbetalipoproteinemia, remnant removal disease or familial broad beta disease.

Pathogenesis:

The hyperlipidemia is caused by the accumulation of chylomicron remnants and IDL. The mutation responsible for this disease involves the gene that encodes the structure of apoprotein E, which binds with very high affinity to both the chylomicron remnant receptor and the LDL receptor, thus it mediates the uptake of those particles by the liver.

The gene for apo E has the alleles designated E^2, E^3, and E^4 and create six genotypes. Type III occurs only in individuals who are homozygous for the E^2 allele (genotype E2/E2). The protein produced by the E2 allele is defective in its ability to bind to the liver receptors, as a result of which these particles accumulate in the plasma.

Clinical manifestations:

Two types of xanthomas are observed in this disease:

- one formn, called xanthoma striata palmaris, developed of the palms and fingers
- the second: tubero-eruptive xanthomas, located at pressure joints as the elbow

Accelerated lipid deposition also occurs in arteries to produce progressive ATS and its sequelae. Associated abnormalities include glucose intolerance or diabetes and obesity.

Diagnosis:

1. the plasma is lactescent and the chylomicron-test may be positif
2. hyperchol and TG
3. broad beta band on lipoprotein electrophoresis from the pre beta position to beta position because of the presence of remnant particles and IDL.

Familial hypertriglyceridemia (Type IV Pattern)

The hyper TG is due to elevated levels of VLDL.

Pathogenesis:

Familial hypertriglyceridemia is transmitted as an autosomal dominant trait, implying a mutation in a single gene. Some patients with familial hyper TO seem to have an underlying defect in the ability to catabolize the TG of VLDL. The nature of the genetic defect has not been determined.

Clinical manifestations:

- obesity
- hyperglycemia
- hypertension
- hypeuricemia

The hyper TG call be aggravated by several factors including poorly controlled diabetes, hypothyroidism, alcohol consumption.

Diagnosis:

1. the plasma is turbid
2. hyper TG
3. LP electrophoresis: the pre beta band is increased

Mixed hyperlipidemia (type V lipoprotein patterns)

This type is associated with an elevation in ch and VL1DL levels. It is considered both an exogenous and endogenous hyper TG.

Diagnosis:

The plasma is lactescent and the Ch-test is positiv.

Hyper TG and chol.

Lipoprotein electrophoresis: the Ch and pre-beta bands are increased,

It may be an excerbated period of type IV hyperlipidemia pattern.

Secondary hyperlipoproteinemias

1. Alcohol consumption

Hepatic metabolism of ethanol by specific enzymes results in high level of acetyl-CoA and NADPH2 which inhibit oxidation of free fatty acids. The excess triglycerides accumulate in the liver, producing, the characteristic enlarged fatty liver of alcoholics. The remainder of the endogenous triglyceride is secreted into plasma, resulting in an increased secretion VLDL (type IV pattern). In those who develop massive alcoholic hyperlipidemia, there appears to be a partial defect in the catabolism of these VLDL particles.

As the concentration of VLDL increases, the VLDL begins to compete with chylomicrons for hydrolysis by lipoprotein lipase, and the plasma concentration of chylomicrons also rises (type V patern).

2. Diabetes mellitus

The relative lack of insulin or insulin resistance for many weeks or months results in a decreased lipoprotein-lipase activity and a reduced capacity of VLDL and chylomicrons catabolism. So the patients develop type IV or V patterns over prolonged period.

Patients with acute insulin deficiency may develop acute ketoacidosis resulting from lipolysis in adipose tissue to form free fatty acids, followed by their oxidation in the liver to from acetyl-CoA. Ineffective Krebs cycle because of insulin deficiency results in transformation of acetyl-CoA to keton bodies.

Diabetes mellitus and a primary from of hyperlipemia may also coexist in the same patient, and thus the diabetes may aggravate the clinical manifestations of the hyperlipoproteinemia.

3. Endocrine disorders

Hypothyroidism is associated with reduced biliary excretion of cholesterol and bile acids resulting in hypercholesterolemia. Low level of thyroid hormones may also result in lack of feed-back inhibition of hepatic cholesterol synthesis by exogenous cholesterol because of decreased number or affinity of LDL-receptors.

Hyperthyroidism (and also high level of cathecolamines) is associated with increased activity of adipous lipase and high level of free fatty acids. They may be utilized for synthesis of VLDL in the liver.

Cushing's syndrome (or glucorticoid intake) may result in increased transformation of Acetyl-CoA to cholesterol, increased secretion of VLDL with conversion to LDL and insulin resistance.

Acromegaly may be also associated with increased secretion of VLDL and insulin resistance.

4. *Dietary influences*

High dietary cholesterol supresses hepatic-LDL-receptor activity and raise the cholesterol level.

Excess caloric consumption promotes obesity and increases VLDL production by the liver with secondary conversion to LDL via IDL.

5. Renal disorders

Uremia may be accompanied by decreased catabolism of VLDL due to reduced lipoprotein lipase activity and insulin resistance.

Nephrotic syndrome is characterized by albuminuria and hypoalbuminuria. The diminished plasma oncotic presssure appears to stimulate hepatic lipoprotein synthesis. Low density lipoproteins and cholesterol are elevated most frequently. Excessive urinary losses of plasma protein factors regulating lipoprotein synthesis or disposal (heparin, apoproteins) may also contribute to the hyperlipidemic state.

I.8. PATHOPHYSIOLOGY OF CARBOHYDRATE METABOLISM

I.8.1. Insulin / Glucagon ratio and the metabolic map in well fed state and starvation

Carbohydrate metabolism is governed by **insulin** and its counterregulatory hormones (epinephrine, growth hormone, cortisol, and glucagon). Of these hormones **glucagon** seems to be the most important. The pattern of metabolism at a certain moment depends basically on insulin/glucagon ratio. Two physiological states are most relevant: well-fed state and starvation. In the former case the insulin:glucagon ratio favors insulin whereas in the latter it favors glucagon.

The metabolic map and the way insulin and glucagon influence biochemical processes will be briefly described for both of these cases. Their pathophysiologic relevance will be made clear later as a substantial support in the understanding of the metabolic alterations in diabetes.

Metabolism in the well fed state: dominant insulin effects

In the absorptive state (2- to 4-hour period after ingestion of a normal meal) there is a transient increase in plasma glucose, amino acids, and tryacylglycerol. Islet tissue of pancreas responds to the elevated levels of glucose and aminoacids with an increased secretion of insulin and a drop in release of glucagon. The elevated insulin to glucagon ratio and the ready availability of circulating substrates make the 2 to 4 hour after ingestion of a meal into an anabolic period characterized by increased synthesis of tryacylglycerols, glycogen, and protein. During this absorptive period virtually all tissues use glucose as a fuel, and the metabolic response of the body is dominated by alterations in the metabolism of liver, adipose tissue, muscle, and brain.

Liver: nutrient distribution center

During the absorptive period the liver takes up carbohydrates, lipids, and the most aminoacids. These nutrients are then metabolized, stored, or routed to other tissues. Thus, the liver smoothes out potentially broad fluctuations in the availability of nutrients for the peripheral tissues.

Carbohydrate metabolism

The glucose transport into the hepatocyte is not influenced by insulin. After a meal hepatic metabolism of glucose is increased by the following mechanisms:

- Increased phosphorylation of glucose
- Increased glycogen synthesis

- Increased glycolysis
- Decreased gluconeogenesis

Fat metabolism

- Increased fatty acid synthesis: Liver is the primary tissue for de novo synthesis of fatty acids. This pathway does occur in the absorptive period because the dietary energy intake exceeds energy expenditure by the body.
- Increased triacylglycerol synthesis: The liver packages triacylglycerols into very low density lipoprotein (VLDL) particles that are secreted into the blood for use by extrahepatic tissues, particularly adipose and muscle tissue.

Aminoacid metabolism

- Increased aminoacid degradation
- Increased protein synthesis

ADIPOSE TISSUE: ENERGY STORAGE DEPOT

A. Carbohydrate metabolism

- Increased glucose transport: Glucose transport into adipocytes is very sensitive to the concentration of glucose in the blood. Circulating insulin is increased in the absorptive state resulting in an influx of glucose into adipocytes.
- Increased glycolysis; in adipose tissue, glycolysis serves a synthetic function by supplying glycerol phosphate for triacylglycerol synthesis

B. Fat metabolism

- Increased synthesis of fatty acids: de novo synthesis of fatty acids in the adipose tissue is not important in humans
- Increased triacylglycerol synthesis
- Decreased triacylglycerol degradation: Elevated insulin favors the dephosphorylated and inactive state of hormone-sensitive lipase. Triacylglycerol degradation is thus inhibited in the well-fed state.

SKELETAL MUSCLE

A. Carbohydrate metabolism

- Increased glucose transport: Glucose is phosphorylated to glucose 6-phosphate and metabolized to provide the energy needs for the cells. This contrasts with the postabsorptive state in which ketone bodies and fatty acids are the major fuels of resting muscles

B. Fat metabolism

- Fatty acids are released from chylomicrons and VLDL by the action of lipoprotein lipase. However, fatty acids are of secondary importance as a fuel for muscle in the well-fed state in which glucose is the primary source of energy.

C. Amino acid metabolism

- Increased protein synthesis
- Increased uptake of branched-chain amino acids

BRAIN

Because brain is vital to the proper function of all organs of the body, special priority is given to its fuel needs. Normally glucose serves as primary fuel, because in the fed state the concentration of ketone bodies is too low to serve as an alternate energy source. However, ketone bodies play a significant role during prolonged starvation.

A. Carbohydrate metabolism

- The brain contains no significant stores of glycogen and is therefore completely dependent on the availability of blood glucose.

B. Fat metabolism

- The brain has no significant stores of triacylglycerol, and the oxidation of fatty acids obtained from blood makes little contribution to energy production because fatty acids do not efficiently cross the blood-brain barrier.

METABOLISM IN STARVATION: DOMINANT GLUCAGON AND OTHER COUNTERREGULATORY HORMONE EFFECTS

The decreased insulin to glucagon ratio, and the decreases availability of circulating substrates , makes the period of nutrient deprivation a catabolic period characterized by degradation of triacylglycerol, glycogen and protein. This sets into motion an exchange in substrates among liver, adipose tissue, muscle and brain that is guided by two priorities:

- the need to maintain adequate plasma levels of glucose to sustain energy metabolism of the brain and other glucose-requiring tissues and
- the need to mobilize fatty acids from adipose tissue and ketone bodies from liver to supply energy to all other tissues.

Liver in starvation

Carbohydrate metabolism

The liver first uses glycogen degradation, then gluconeogenesis to maintain blood glucose levels to sustain energy metabolism of the brain and other glucose-requiring tissues.

- Increased glycogen degradation Liver glycogen is nearly exhausted after 10 to 18 hours of fasting and, therefore, hepatic glycogenolysis is a transient response to early starvation.
- Increased gluconeogenesis The carbon skeleton for gluconeogenesis are derived primarily from amino acids, glycerol and lactate. Gluconeogenesis begins four to six hours after the last meal and becomes fully active as stores of liver glycogen are depleted.

Fat metabolism

- Increased fatty acid oxidation is the major source of energy in hepatic tissue in the postabsorptive state
- Increased synthesis of ketone bodies. Liver is unique in being able to synthesize and release ketone bodies (primarily hydroxybutirate) for use as fuels by peripheral tissues. Ketone body synthesis is favored when the concentration of acetyl-CoA, produced from fatty acid metabolism exceeds the capacity of the Krebs cycle. The availability of circulating ketone bodies is important in starvation because they can be used for fuel by most of the tissues including brain, once their level in the blood is sufficiently high. This reduces the need for gluconeogenesis from acid carbon skeletons, thus slowing the loss of essential protein.

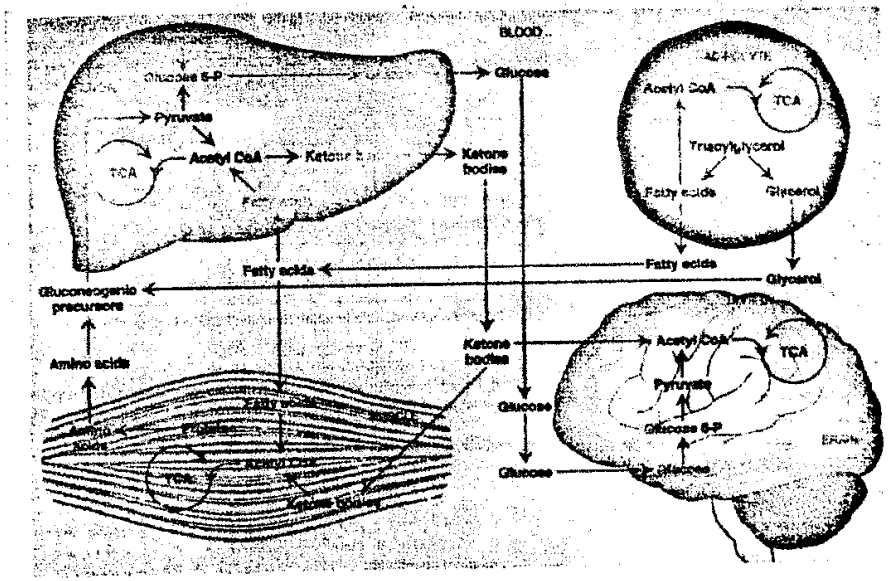


Figure no. 9
Intertissue relationships during starvation
(the metabolic map resembles the situation of diabetes mellitus)

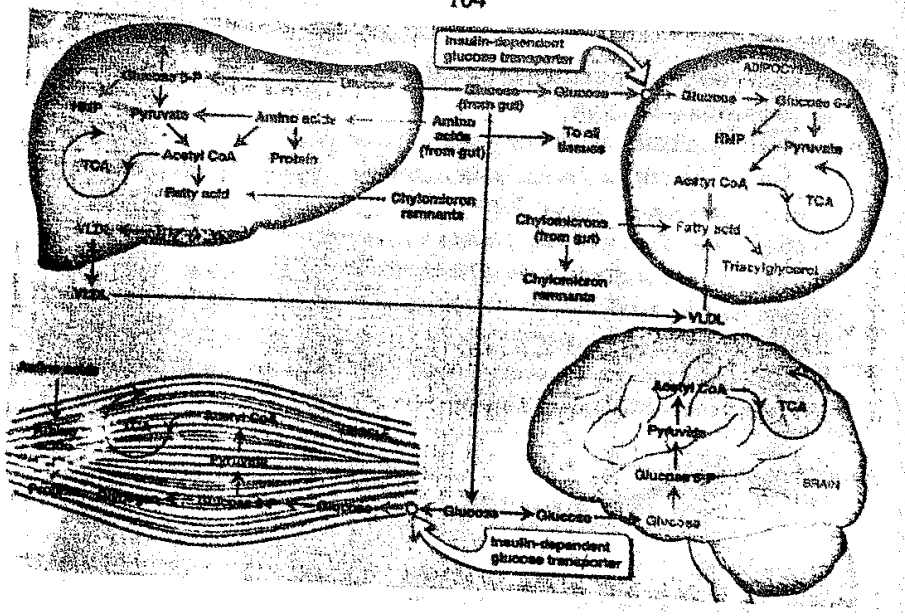


Figure no. 10
Intertissue relationships in the postabsorbtive state

ADIPOSE TISSUE IN STARVATION

Carbohydrate metabolism

- Glucose transport into the adipocyte and its subsequent metabolism are depressed owing to low levels of circulating insulin. This leads to decrease in fatty acid and triacylglycerol synthesis.

Fat metabolism

- Increased degradation of triacylglycerols. The activation of hormone-sensitive lipase and subsequent hydrolysis of stored triacylglycerol are enhanced by the elevated cathecolamines.
- Increased release of fatty acids: Fatty acids obtained from hydrolysis of stored triacylglycerol are released into the blood and transported to a variety of tissues for use as fuels. The glycerol produced following triacylglycerol degradation is used as gluconeogenic precursor by the liver.
- Decreased uptake of fatty acids: In starvation, lipoprotein lipase activity of adipose tissue is low. Consequently, circulating triacylglycerol of lipoproteins is not available for triacylglycerol synthesis in adipose tissue.

SKELETAL MUSCLE IN STARVATION

Carbohydrate metabolism

- Glucose transport into skeletal muscle cells via insulin-dependent glucose transport and subsequent glucose metabolism is depressed because of low levels of circulating insulin.

Lipid metabolism

- Muscle uses fatty acids from adipose tissue and ketone bodies from the liver as fuels.

Protein metabolism

- During the first days of starvation there is rapid breakdown of muscle protein, providing aminoacids that are used by the liver for gluconeogenesis. After several weeks of starvation the rate of muscle proteolysis decreases owing to a decline in the need of glucose as a fuel for brain.

BRAIN IN STARVATION

During the first days of starvation, the brain continues to use glucose as a fuel exclusively. In prolonged starvation plasma ketone bodies reach markedly elevated levels and are used as a fuel by the brain. This reduces the need for protein catabolism for gluconeogenesis.

DIABETES MELLITUS

Diabetes is not one disease but rather is a heterogeneous group of syndromes characterized by an elevation of fasting blood glucose caused by a relative or absolute deficiency in insulin. Metabolic alterations caused by inadequate release of insulin are aggravated by an excess of glucagon. Fat and protein metabolism are also commonly affected.

CLASSIFICATION

There is a primary or idiopathic diabetes mellitus, which is by far the most common and important entity, and secondary diabetes which includes forms of hyperglycemia associated with identifiable causes either pancreatic or endocrine.

1. Primary or spontaneous DM, including over 90% of cases, is a heterogeneous class that may be subdivided into :
   - type I or insulin-dependent DM (IDDM)
   - type II or non-insulin-dependent DM (NIDDM)
2. Secondary DM, including conditions associated with the development of diabetes, also subdivided into two types:

- DM associated with other endocrine disorders, such as Cushing's disease, pheochromocytoma, acromegaly or the glucagonoma syndrome, in which there is

excessive production of hormones countering the actions of insulin
- DM associated with pancreatic disease, following e.g. total pancreatectomy performed for carcinoma, or chronic pancreatitis e.g. in alcoholics, hemochromatosis or cystic fibrosis.

ETIOLOGY AND PATHOGENESIS OF TYPE I DIABETES

The disease is characterized by an absolute deficiency of insulin caused by massive autoimmune attack on the cells of the pancreas. This destruction requires a stimulus from the environment (such as a viral infection) and a genetic determinant that allows -cells to be recognized as "nonself". At least one of the susceptibility genes for IDDM resides in the genes encoding the class II antigens of the major histocompatibility system (HLA-D). There seems to be an ordered hierarchy of susceptibility associated with the various class II genes. By far the most common is the HLA-DQ3.2 which is present in 70% of the patients. Individuals bearing these gene have an eightfold risk of developing IDDM compared with those not carrying the gene. The precise mechanism by which these haplotypes influence the risk of IDDM is still unclear. It seems likely that several clusters of distinct aminoacids affect interactions between the DQ molecule and its bound peptide (antigen) or interactions with the T-cell receptor or both, somehow facilitating the development of autoimmunity. The islets of Langerhans become infiltrated with activated T-lymphocytes, leading to a condition called **insulitis**. Over a period of years this autoimmune attack leads to a gradual depletion of the β-cell population. However, symptoms appear abruptly when 80-90% of the β-cells have been destroyed. At this point pancreas fails to respond to ingestion of glucose, and insulin therapy is required to restore metabolic control.

ETIOLOGY AND PATHOGENESIS OF TYPE II DIABETES

NIDDM is by far the most common type. Genetic factors are even more important than in type I diabetes, because among identical twins, the concordance rate is more than 90%. Unlike IDDM, the disease is not linked to any HLA genes, and there is no evidence that autoimmune mechanisms are involved.. The metabolic alterations observed in NIDDM are milder than those described for the insulin-dependent form of disease and are thought to be due to a combination of two factors: dysfunctional β-cells and insulin resistance.

Dysfunctional β-cells

In NIDDM, the pancreas retains β-cell capacity, resulting in insulin levels that vary from below normal to above normal. However, in all cases, the β-cell is

dysfunctional because it fails to secrete enough insulin to correct the prevailing hyperglycemia. For example, insulin levels are high in typical obese NIDDM patients, but not as high as in nondiabetic but similarly obese individuals. The cause of insulin deficiency in type II diabetes is unknown. Unlike type I diabetes, there is no evidence for viral or immune-mediated injury to the islet cells. According to one view, all the somatic cells of diabetics, including pancreatic β-cells, are genetically vulnerable to injury, leading to accelerated cell turnover and premature aging and, ultimately, to a modest reduction in β-cell mass.

Insulin resistance

Insulin resistance occurs when tissues fail to respond normally to insulin. Type II diabetes is frequently accompanied by target organ insulin resistance that results in a decreased responsiveness to both endogenous and exogenous insulin. For example resistance in the liver leads to uncontrolled hepatic glucose production, whereas resistance in muscle and adipose tissue results in decreased glucose uptake by these tissues. Insulin resistance in type II diabetes mellitus may be due to any of a number of defects in signal transduction, ranging from abnormal insulin receptors to defects in glucose transporters.

Note: Over 80% of patients with NIDDM are obese. This is significant because insulin resistance is in part due to the effect of obesity. Glucose tolerance in obese patients with NIDDM markedly improves with weight reduction.

TYPE I VS. TYPE II DIABETES

	IDDM (TYPE I)	NIDDM (TYPE II)
Clinical	Onset < 20 years	Onset > 30 years
	Normal weight	Obese
	Decreased blood insulin	Normal or increased blood insulin
	Islet cell antibodies	No islet cell antibodies
	Ketoacidosis common	Ketoacidosis rare
Genetics	50% concordance in twins	90 -100% concordance in twins
	HLA-D linked	No HLA association
Pathogenesis	Autoimmunity	Insulin resistance
	Immunopathologic mechanisms	Relative insulin deficiency
	Severe insulin deficiency	
Islet cells	Insulitis early	No insulitis
	Marked atrophy and fibrosis	Focal atrophy and amyloid
	Beta-cell depletion	Mild beta-cell depletion

METABOLIC FEATURES OF DIABETES MELLITUS

Insulin is a major anabolic hormone in the body and therefore derangement of insulin function affects not only glucose metabolism but also fat and protein metabolism. All pathways of intermediary metabolism are disrupted to a greater or lesser degree in patients with DM (Fig. 11). Unopposed secretion of counter-regulatory hormones (glucagon, growth hormone, epinephrine) is now thought to play a role in these metabolic derangements, which are most severe in type I diabetes.

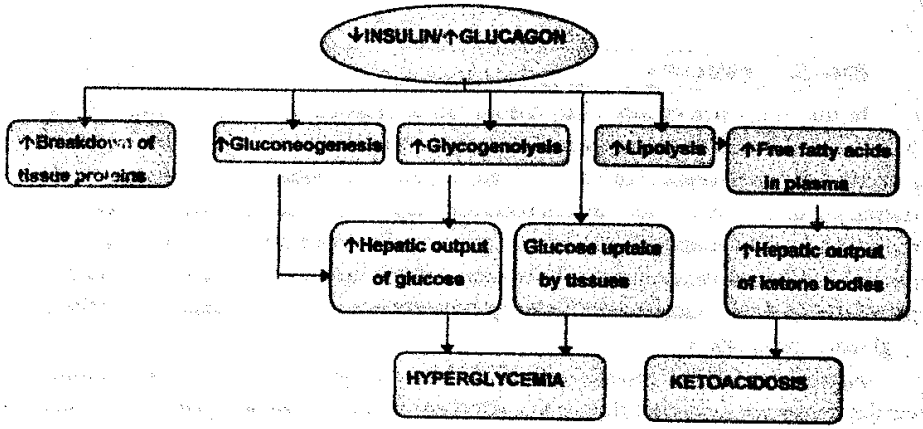


Figure no. 11

Metabolic changes in diabetic mellitus due to impaired insulin/glucagon ratio

Hyperglycemia and ketoacidosis are the hallmarks of untreated diabetes mellitus. Hyperglycemia is caused by increased hepatic production of glucose combined with diminished peripheral utilization and when above glucose renal threshold, glycosuria ensues, accompanied by osmotic diuresis, polyuria and subsequent loss of water and electrolytes. Water loss combined with hyperosmolarity resulting from hyperglycemia depletes intracellular water, e.g. in the osmoreceptors of the thirst center in the brain. This results in compensatory water intake - polydipsia.

Ketosis results from increased mobilization of fatty acids from adipose tissue combined with accelerated hepatic synthesis of hydroxybutyrate and acetoacetate. However, not all the fatty acids flooding the liver can be disposed of through oxidation or ketone body synthesis. Fatty acids are also converted to triacylglycerol, which is packaged and secreted in VLDL. Chylomicrons are synthesized from dietary lipids by the intestinal mucosal cells following a meal. Because lipoprotein degradation catalyzed by lipoprotein lipase in adipose tissue is low in diabetics, the

plasma chylomicrons and VLDL levels are elevated resulting in hypertriglyceridemia. These metabolic changes result from a deficiency of insulin and a relative excess of glucagon, the latter playing a critical role in stimulating gluconeogenesis and ketogenesis.

CLINICAL FEATURES

Clinical features of untreated DM are the result of the metabolic disorders. Intense thirst (polydipsia) results from alterations of brain thirst centers. Through poorly defined pathways, increased appetite (polyphagia) develops, thus completing the classical triad of diabetic findings - polyuria, polydipsia and polyphagia. Fat and muscle are also exhausted to provide energy requirements and thus the patient loses weight. Hyperglycemia reduces the resistance to bacterial infections, causes itching, and leads to glycosuria. Long standing DM often leads to intercapillary glomerulosclerosis (the Kimmelstiel-Wilson lesion in the kidney), which is accompanied by proteinuria and renal failure.

LATE COMPLICATIONS OF DIABETES

The morbidity associated with long-standing diabetes of either type results from complications such as microangiopathy, retinopathy, nephropathy, and neuropathy. Despite a few views suggesting these complications to be a genetic concomitant unrelated to the metabolic abnormalities, most scientists assert them as being a consequence of the metabolic derangements. Since hyperglycemia is the most obvious and consistent metabolic abnormality in DM, many mechanisms that link hyperglycemia to the complications of long standing diabetes have been explored. Currently, two such mechanisms are considered important:

1. Nonenzymatic Glycosylation

This is the process by which glucose chemically attaches to the amino group of proteins without the aid of enzymes. Glucose forms chemically reversible glycosylation products with protein which rather than dissociating, undergo a slow series of chemical rearrangements to form irreversible advanced glycosylation end products (AGE), which accumulate over the life-time of the vessel wall. AGEs have a number of chemical and biologic properties which are potentially pathogenic.

NEG is proportional to blood glucose levels. NE glycosylation of hemoglobin A (HbA) occurs continuously over the 120-day life span of the red cell and leads to the formation of HbA1c, that provides an index of the average blood glucose over the preceding 2 to 4 months. HbA1c constitutes about 4% of the red cells hemoglobin in normal individuals while it is much increased in DM patients.

RELEVANT CHEMICAL AND BIOLOGIC PROPERTIES OF ADVANCED GLYCOSYLATION END PRODUCTS

Chemical

- Cross-link polypeptides of same protein (e.g. collagen)
- Trap nonglycosylated proteins (e.g. LDL, Ig, complement)
- Confer resistance to proteolytic digestion
- Induce lipid oxidation
- Inactivate nitric oxide

Biologic

Bind to AGE receptors on monocytes and mesenchymal cells

Induce: Monocyte emigration

Cytokines and growth factor secretion

Increased vascular permeability

Procoagulant activity

Enhanced cellular proliferation

Enhanced extracellular matrix production

- AGE formation occurs on proteins, lipids, and nucleic acids. On proteins, such as collagen, they cause cross-links between polypeptides of the collagen molecule and also trap nonglycosylated plasma or interstitial proteins. In large vessels trapping of low-density lipoproteins (LDL), for example, retards its efflux from the vessel wall and enhances the deposition of cholesterol in the intima, thus accelerating atherogenesis. In capillaries, including those of renal glomeruli, plasma proteins such as albumin bind to glycosylated basement membrane, accounting in part for the increased basement membrane thickening characteristic of diabetic microangiopathy. AGE cross-linked proteins are resistant to proteolytic digestion. Thus, cross-linking decreases protein removal while enhancing protein deposition. AGE-induced cross-linking in collagen in basement membrane may also impair the interaction of collagen with other matrix components (laminin, proteoglycans), resulting in structural and functional defects in the basement membrane.
- AGEs bind to receptors on many cell types - endothelium, monocytes, macrophages, lymphocytes and mesangial cells. Binding induces a variety of biologic activities, including monocyte emigration; release of cytokines and growth factors from macrophages; increased endothelial permeability; increased procoagulant activity on endothelial cells and macrophages; and enhanced proliferation of and synthesis of extracellular matrix by fibroblasts

and smooth muscle cells. All these effects can potentially contribute to diabetic complications.

2. Intracellular Hyperglycemia With Disturbances In Polyol Pathways

In some tissues that do not require insulin for glucose transport (nerves, lens, kidneys, and blood vessels), hyperglycemia leads to an increase in intracellular glucose. Glucose excess is metabolized to sorbitol and secondary to fructose. The accumulation of these two products results in an increased intracellular osmolarity and influx of water, and, eventually, to osmotic cell injury. In the lens, osmotically imbibed water causes swelling and opacity. Second, sorbitol accumulation is associated with a decrease in the myoinositol content resulting in decreased phosphoinositide metabolism, diacylglycerol, protein kinase C, and Na^+ / K^+ ATP-ase activity. This mechanism may be responsible for damage to Schwann cells and retinal capillaries pericytes, that results in peripheral neuropathy and retinal microaneurysms. These pathways contribute to the ocular and neurologic complications of DM.

Acute metabolic complications

In addition to hypoglycemia, diabetics are susceptible to two major acute metabolic complications: diabetic ketoacidosis and hyperosmolar, nonketotic coma. The former is a complication of insulin-dependent diabetes, while the latter usually occurs in the setting of non-insulin dependent disease. Ketoacidosis rarely, if ever, develops in true type two diabetes.

1. Diabetic ketoacidosis

Ketoacidosis is a state of uncontrolled catabolism associated with insulin deficiency and relatively excess of glucagon and epinephrine. Its main causes can be grouped as follows:

- Previously undiagnosed diabetes
- Interruption of insulin therapy
- The stress of intercurrent illness

The altered hormonal state (↓insulin/↑glucagon) has the following consequences (Fig. 12):

- Maximal gluconeogenesis and impaired peripheral utilization of glucose. The resultant hyperglycemia and osmotic diuresis leads to volume depletion and dehydration that characterize the ketoacidotic state. As a consequence plasma osmolality rises and renal perfusion falls which further aggravates acidosis due to depressed excretion of hydrogen ions and ketones.
- Activate the ketogenic process and thus initiate the development of metabolic acidosis. For ketosis to occur, changes must be produced in both adipose

tissue and the liver. Free fatty acids from the adipose tissue represent the primary substrate for ketone body formation. Their plasma levels must rise if ketogenesis are to develop. At the same time, the hepatic oxidative machinery for fatty acids is activated.

While free fatty acid release is enhanced directly by insulin deficiency, accelerated fatty acid oxidation in the liver is primarily induced by glucagon, via action on the carnitine palmitoyl transferase system of enzymes responsible for the transport of fatty acids into the mitochondria.

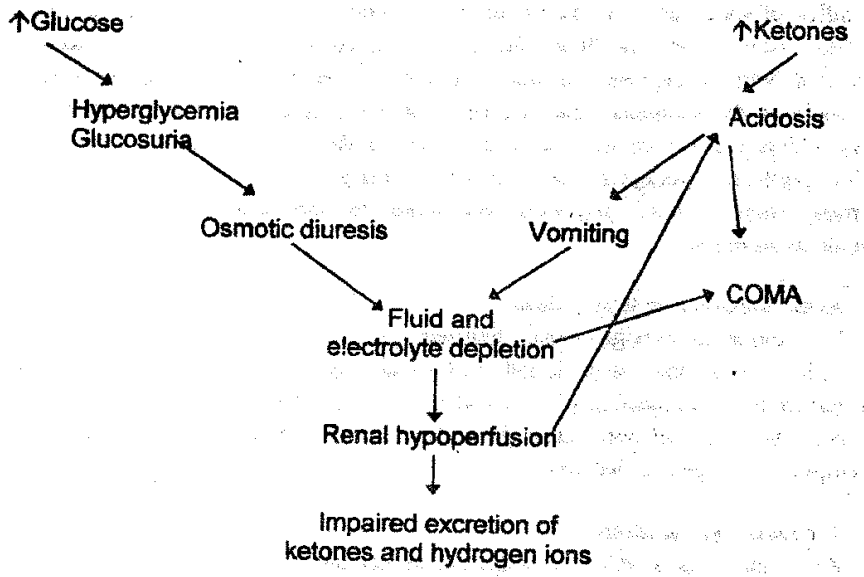


Figure no. 12
Pathophysiologic events in diabetic ketoacidosis

Overproduction of ketones by the liver is the primary event in ketotic states, but limitation in peripheral utilization also play a role at high concentrations of acetoacetate and β-hydroxybutyrate.

The metabolic acidosis is almost totally accounted for by the elevated plasma levels of acetoacetate and β-hydroxybutyrate.

Despite initial potassium concentrations that are normal to high there is a total body potassium deficit due to urinary loss. The serum sodium concentration tends to be low because of the hyperglycemia that draws intracellular water into the plasma space.

- **Clinical manifestation**

The features of ketoacidosis are those of uncontrolled diabetes with acidosis, and include prostration, hyperventilation (Kussmaul respiration), nausea, vomiting and, occasionally, abdominal pain. About 5% of the patient present in coma. Evidence of marked dehydration is present and the eyeball is lax to pressure in severe cases. Hyperventilation is present and the smell of ketones on the breath allows an instant diagnosis. The skin is dry and the body temperature is often subnormal.

- **Diagnosis** is confirmed by demonstrating hyperglycemia with ketonemia and heavy ketonuria, and acidosis.

2. Hyperosmolar Coma

Hyperosmolar nonketotic coma is usually a complication of non-insulin-dependent diabetes. It is a syndrome of profound dehydration resulting from a sustained hyperglycemic diuresis under circumstances in which the patient is unable to drink sufficient water to keep with urinary fluid losses. Commonly an elderly diabetic develops a stroke or infection, which worsens hyperglycemia an prevents adequate water intake.

The absence of ketoacidosis is important in the pathophysiology.

The biochemical differences between non-ketotic coma and ketosis may partly be explained as follows:

- The extreme dehydration characteristic of non-ketotic coma may be related to age. Old people experience thirst less acutely, and more readily become dehydrated. In addition, the mild renal impairment associated with age results in increased urinary losses of fluid and electrolytes.
- The degree of insulin deficiency is less severe in non-ketotic coma. Endogenous insulin levels are sufficient to inhibit hepatic ketogenesis, whereas glucose production is unrestrained.

Clinical presentation

The characteristic clinical features are dehydration and stupor or coma. Impairment of consciousness is directly related to the degree of hyperosmolality. Evidence of an underlying illness such as pneumonia or pielonephritis may be present, and the hyperosmolar state may predispose to stroke, myocardial infarction or arterial insufficiency in the lower limbs.

3. Hypoglycemia In IDDM

One of the therapeutic goals of diabetes is to increase blood glucose levels in an effort to minimize the development of the long-term complications of the disease. However, appropriate dosage is difficult to achieve in all patients and hypoglycemia is the most common complication of insulin therapy, occurring in over 90% of the

patients. The frequency of hypoglycemia episodes, coma and seizures is particularly high with intensive treatment regimens designed to achieve tight control of blood glucose. It is known that in normal individuals hypoglycemia triggers a compensatory secretion of counterregulatory hormones, most notably glucagon and epinephrine, which promote hepatic production of glucose. However, patients with IDDM also develop a deficiency of glucagon secretion. This defect occurs early in the disease and is almost universally present 4 years after diagnosis. These patients thus relies on epinephrine secretion to prevent severe hypoglycemia. However, as the disease progresses IDDM patients show diabetic autonomic neuropathy and impaired ability to secrete epinephrine in response to hypoglycemia. The combined deficiency of glucagon and epinephrine secretion makes these patients with long-standing diabetes particularly vulnerable to hypoglycemia.

HYPOGLYCEMIA

Symptoms of hypoglycemia usually occur with plasma glucose levels below 50 mg/dl. Hypoglycemia is dangerous (in short run more dangerous than hyperglycemia) because glucose is the primary energy substrate for the brain. Its absence, like that of oxygen, produces deranged function, tissue damage, or even death if the deficit is prolonged.

SIMPTOMATOLOGY

Symptoms of hypoglycemia fall into two main categories: those induced by an excessive excretion of epinephrine and those due to the dysfunction of the central nervous system.

Rapid epinephrine release causes sweating, tremor, tachycardia, anxiety and hunger.

Central nervous system symptoms include dizziness, headache, clouding of vision, blunted mental acuity, loss of fine motor skill, confusion, abnormal behavior, convulsions, and loss of consciousness.

The level of plasma glucose required to impair metabolism is not uniform. In nondiabetic persons acute lowering of plasma glucose to around 50 mg/dl produces autonomic nervous system symptoms and induces release of counterregulatory hormones. Poorly controlled patients with diabetes appear to develop symptoms at higher glucose concentration.

CLASSIFICATION

Hypoglycemia is classified as either postprandial (reactive) or fasting. Pathologically low plasma glucose concentrations occur in the former only in response to meals, while in the latter only after a fasting for a few to many hours.

POSTPRANDIAL HYPOGLYCEMIA

The most common cause of postprandial hypoglycemia is alimentary hyperinsulinism. Patients who have undergone gastrectomy, gastrojejunostomy, pyloroplasty, or vagotomy are subject to hypoglycemia following meals presumably because of rapid gastric emptying with brisk absorption of glucose and excessive insulin release.

FASTING HYPOGLYCEMIA

The causes of fasting hypoglycemia are many, but in all there is an imbalance between the production of glucose by the liver and its utilization in peripheral tissues. In some, hypoglycemia is due primarily to a defect in glucose production, while in others the problem is excess glucose utilization. Both defects may be present. For example, with insulin excess there is driven glucose utilization coupled with blunted hepatic glucose production. The latter is caused by insulin's capacity to block the glycogenolytic/gluconeogenetic effects of counterregulatory hormones.

UNDERPRODUCTION OF GLUCOSE

The production of the glucose by the liver initially involves the breakdown of stored glycogen and subsequently depends on gluconeogenesis.

The causes of inadequate production can be grouped into five categories:

1. hormone deficiencies
2. defects in glycogenolytic and gluconeogenic enzymes
3. inadequate substrate delivery
4. liver disease
5. drugs

- Hypopituitarism and adrenal insufficiency are the most common of the hormone deficiency states causing hypoglycemia
- Enzymatic abnormalities causing hypoglycemia are generally seen in children not in adults. Glucose-6-phosphatase deficiency is the classic example of a defect in glycogen breakdown, but hypoglycemia may occur in young children with deficiencies of hepatic glycogen phosphorilase and in other forms of glycogen storage disease.
- Acquired liver disease can cause serious hypoglycemia. Hepatic congestion due to right-sided heart failure is particularly troublesome, but severe viral hepatitis or cirrhosis may also cause symptomatic hypoglycemia.
- A number of drugs cause hypoglycemia. The most common, apart from insulin and sulfonylureas, is alcohol. Alcohol induces hypoglycemia only after a period of fasting sufficient to deplete liver glycogen stores. In this circumstance hepatic glucose production is dependent on gluconeogenesis. The oxidation of ethanol in the liver is accompanied by generation of NADH,

the reduced form of nicotinamide adenine nucleotide (NAD) , in the cytosol of the cell. The increased NADH/NAD ratio diverts oxalacetate into malate formation, diminishing its availability to gluconeogenesis. Large amounts of ethanol are not required to produce this syndrome.

Overutilization Of Glucose

Overutilization of glucose occurs in two settings. In the first, hyperinsulinism is present, and in the second, plasma insulin concentrations are low. There basic causes of hyperinsulinemic hyperglycemia:

- insulinoma
- exogenous insulin administration
- sulfonylureas

Hypoglycemia in the context of glucose overutilization and appropriately low plasma insulin concentrations occurs in two situations. The first is in association with solid extrapancreatic tumors, usually of large size. The most common are of mesothelial origin and include fibromas and sarcomas. The mechanism of hypoglycemia is not clear , although high levels of insulin-like growth factors may play a role. Presumably such factors, if present, act via the insulin receptor rather than binding to their own receptors.

Symptomatic hypoglycemia due to overutilization may also occur in situations where free fatty acids and ketones are not available for oxidation in muscle and other tissues. Patients with systemic carnitine deficiency may have severe hypoglycemia. In this condition carnitine, which is necessary to transport fatty acids into mitochondria for oxidation, is low in plasma muscle, liver, and other tissues. As a result, peripheral tissues cannot utilize fatty acids for energy production, and liver cannot make ketone bodies as alternative substrate. The result is that all tissues become glucose-dependent, exceeding the capacity of liver to meet the demand.

I.9. PATHOPHYSIOLOGY OF WATER AND ELECTROLYTE BALANCE

I. PHYSIOLOGY

I.1. WATER

Total water

- male 60% of total body weight
- female 50% of total body weight
- new-born infants 70% of total body weight

I.2. DISTRIBUTION OF WATER: 2 compartments (for a 70 kg man = 42 liters)

1. *Intracellular*: 40% of total body weight (30 l)
2. *Extracellular*: 20% of total body weight (12 l)
   15% volume of interstitial fluids (9 l)
   5% plasma volume (3 l)

I.3. ELECTROLYTES:

Distribution of ions:

1. *Intracellular:* dominant cation: K+
   dominant anions: proteins, organic acids, organic phosphate
2. *Extracellular:* dominant cation: Na+
   dominant anion: Cl-

Interstitial fluid - very low protein concentration (less than 1 g/l)
Intravascular fluid - high protein content (70 g/l)

Protein acts as an anion, so diffusible anions are at a lower concentration in plasma than in interstitial fluid, whilst the opposite is true for diffusible cations: this is known as the Gibbs-Donnau equilibrium. However, the affect is small and the measurement of plasma electrolyte concentrations may be used to asses those of the ECF as a whole.

OSMOLALITY

The osmotic pressure created by a solution is proportional to the number of solute that area present; it is not related to the size of particle. This property is the osmolality of the solution and is expressed as mmol/kg. The normal plasma osmolality is 280-300 mmol/kg water.

Oncotic pressure described the pressure exerted by proteins across cell membrane. The extent of the oncotic pressure is small by comparison with osmotic

pressure and becomes of physiological importance in the capillary bed which is permeable to those particles (cations and anions) that exert osmotic pressure.

While the transfer of water between the compartiments of the body is passive, the distribution of sodium and potassium between intracellular and extracellular compartments depends on active transport mediated by cell membrane ATP-ase.

I.4. THE EXTERNAL BALANCE OF WATER AND SODIUM

Both physiologically and clinically sodium and water metabolism are closelly interrelated. The sodium content of the body depends on the balance between dietary intake and renal excretion of Na. Thus, in normal persons, the sodium content of the body remains quite constant despite wide variations in sodium intake.

CONTROL OF SODIUM METABOLISM

The sodium content of the body is regulated by renal tubular reabsorbtion. This is determined by:

1. renal blood flow
2. angiotensin II
3 aldosterone
4. sympatic nervous system
5. natriuretic hormones

1. The **GFR** tends to increase with volume expansion and decrease with volume depletion, both of which can contribute to the associated changes in Na excretion. However, alterations in the GFR are not required for the maintenance of the Na balance. As an example, patients with then end- stage renal disease may have a substantial reduction in GFR. Neverthless, they are usually able to adjust Na excretion to match intake by decreasing the rate of tubular reabsorbtion.

2. **Angiotensin II** . Renin secretion is enhanced in hypovolemic desorders, resulting in the generation of angiotensin II, which has 2 major actions: it raises the blood pressure by arterial vasoconstriction, and it induces renal Na retention , both directly and by increasing the secretion of aldosterone.

3. **Aldosterone** stimulates reabsorbtion of sodium by the distal renal tubules. Aldosterone also increases the secretion of K+.

4. **Sympathetic nervous system** . Sympathetic neural tone and secretion of catecholamines from the adrenal medulla are reduced by volume expansion and enhanced by volume depletion. This effective volume depletion, due to fluid loss or to reduced tissue perfusion in hepatic cirrhosis or heart failure is associated with increased systemic and renal sympathetic activity.

Renal tubular Na+ reabsorbtion is enhanced because of both a direct adrenergic effect and increases in angiotensinogen II and aldosterone secretion.

5. **Atrial natriuretic peptides (ANP).** Atrial distension due to expansion of intravascular volume release ANP from atrial myocytes. ANP binds to receptors on vascular smooth muscle, the renal tubules, adrenal cortex and the brain; these receptors use cyclic GMP as a second messenger system. It causes vasodilation, natriuresis and inhibition of aldosterone secretion and supression of ADH and renin release.

Because Na is essentially confined to the ECF, total body Na+ content is the determinant of the ECF volume, which is monitored by volume receptors in both high (arterial) and low (venous) pressure locations. Important among these are low pressure receptors in the cardiac atria / or thoracic veins, and high pressure baroreceptors in the carotid sinus and renal juxtaglomerular apparatus. In response to the appropriate signals from such receptors, ECF volume is modulated by changing renal excretion of Na.

CONTROL OF WATER METABOLISM

The water content of the body is regulated by a combination of thirst and ADH secretion.

1. Thirst: the thirst center is located in the lateral preoptic area of the hypotalamus.

Osmotic stimulation

When water is lost the osmolality of the ECF , interstitial and intravascular, increases and stimulates osmoreceptors in the hypotalamus. When the Na concentrations rise approximately 2 mEq/l above normal (or the osmolality rises approximately 4 mOsm/l above normal) the drinking mechanism becomes "tripped", that is, the person then reaches a level of thirst that is strong enough to activate the necessary motor effort to cause drinking. This is called the "threshold for drinking". The person ordinarily drinks precisely the required amount of fluid to bring the ECF to normal. That is to a state of satiety. Because the kidneys are continually excreting fluid and also fluid is lost by evaporation from the skin and lungs, a person is continually being dehydrated. The volume of ECF decreases and its concentration of Na and other osmolar elements rises and after a period of time the drinking act is tripped again.

In this way, both Na concentration and the osmolality of the ECF are very precisely controlled.

Other stimulation

1. Intracellular dehydration: any factor that will cause intracellular dehydration will in general cause the sensation of thirst. The most common cause of this is increased osmolar concentration of the ECF, however, an excessive loss of K+ from the body, which reduces the intracellular K+ of the thirst cells can decrease their volume.

2. Angiotensin II acts on a specialized center located on the surface of the third ventricle.

3. Low cardiac output . Patients with low cardiac output resulting from cardiac failure frequently develop intense thirst.

4. Dryness of the mouth. Probably the same factors that cause intracellular dehydration cause also a dry mouth.

2. ADH

Osmotic stimulation

It is a typical feed-back control system that operates by the following steps:

1. an increase in osmolality excites osmoreceptors located in the supraoptic nuclei of the hypothalamus

2. excitation of the supraoptic nuclei causes the posterior pituitary gland to release ADH

3. the ADH increases the permeability of the late distal tubules, the collecting tubules and the collecting ducts, and therefore causes increased conservation of water by kidneys.

Conversely, when the ECF becomes too dilute (hypoosmotic) less ADH is formed, and excess water is lost in comparison with the ECF solutes, thus concentrating the body fluids back towards normal.

Changes of 2% or less in plasma osmolality can be detected by osmoreceptors in the hypothalamus.

Non-osmotic stimulation

1. Reduction in circulating blood volume and/ or hypotension. Nervous signals from the volume receptors in the heart and also from the baroreceptors control ADH secretion.

A reduction of 10% or more may trigger ADH release even in the absence of changes in plasma osmolality. If volume concentration is sufficiently severe, volume-mediated stimulation of ADH may overvide osmotic signals and cause water retention despite progressive dilution of body fluid. Conversely, extracellular volume expansion tends to suppress ADH release even if the body fluids are hypertonic

2. Other non-osmotic stimuli : nausea and vomiting, hypoglycemia and pain.

The total Na content of the body is determined by the renal sodium regulatory mechanisms described earlier. However, the principal determinant of plasma Na concentration is water metabolism rather than total body Na content. When either ADH mechanism or the thirst mechanism fails, the other ordinarily can still control both Na concentration and ECF osmolality with reasonable effectiveness. On the other hand, if both of them fail simultaneously, neither Na nor osmolality is adequately controlled.

Therefore, the major feedback mechanism for control of Na concentration (and also for extracellular osmolality) is the ADH-thirst mechanisms.

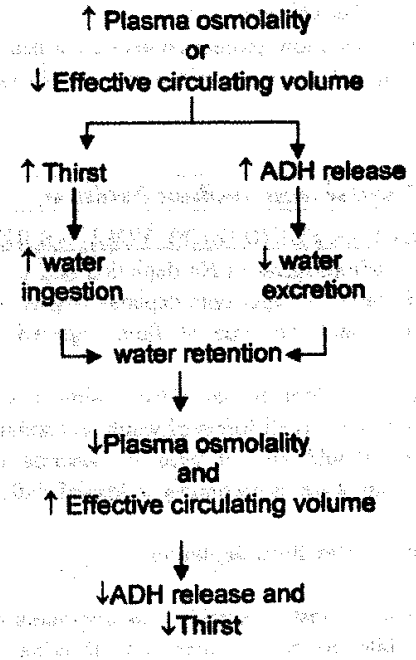


Figure no. 13
The regulatory mechanisms of water balance

5. The internal balance of water and sodium: edema

The capillary endothelium acts as a semipermeable membrane and is highly permeable to water and to almost all solutes in plasma with the exception of proteins. The passage of water across the walls of the small blood vessels is determined by the balance betwen the hydrostatic and oncotic pressures. Normally, fluid is expelled from the arterial end of the microcirculation and reenters at the venous end.

An increase in the hydrostatic pressure or a fall in the plasma oncotic pressure will increase the net flaw of fluid into the interstitial space. Fluid is constantly removed from the interstitial space by the lymphatics and acumulates to cause edema only when the increase in flow cannot be accomodated by the lymphatic drainage. Thus, edema may be caused by increased hydrostatic pressure, decreased plasma oncotic pressure or lymphatic obstruction.

Edema may be localized or generalized. In generalized edema, fluid may also accumulate in the serous cavities. In the peritoneal cavity this is called *ascites*, in the pleural cavity - *hydrothorax or pleural effusion*, and in the pericardial sac, *hydropericardium or pericardial effusion*.

When the edema fluid has a low protein content as in heart failure or nephrotic syndrome it is called a transsudate, in contrast to the protein rich exudate occurs in inflammations.

II. Disorders of water and sodium balance

II.1. EXTRACELLULAR FLUID (ECF). VOLUME DEFICIT

Losses of water and sodium result in Na depletion and ECF volume depletion; whether it is hypotonic, isotonic or hypertonic depends largely upon the route of loss (e.g. gastrointestinal, renal) and the type of fluid ingested by or given to the individual.

Clinical syndromes due to loss of water and sodium are common. The word dehydration is commonly applied to all forms of water and sodium loss, but the word means loss of water and should be not used to describe conditions in which redistribution and loss of body water is secondary to loss of sodium.

II.1.1. Isotonic extracellular fluid depletion

1. Loss of isotonic fluid

Water and sodium may be lost in roughly equal amounts in plasma, secretions from the small intestine, bile, pancreatic juice and the urine passed when tubular function has failed.

2. Removing of ECF

Removing of ECF from the general circulation in pool of fluid without being lost from the body, for example in ascites, gross edema, or paralytic ileus.

Physiopathologic aspects

Under these circumstances aldosterone is secreted in response to volume depletion and sodium is retained by the kidney. The resulting increase in osmolality causes enhanced ADH secretion, maximal water reabsorption in the renal collecting ducts, and oliguria together with thirst. If fluid is unavailable and losses continued, hypovolemia, decreased cardiac output and falling glomerular filtration rate will occur with a rising plasma urea.

II.1.2. Hypertonic extracellular fluid depletion

The syndrome of predominant water depletion develops when fluid intake is insufficient and there is continuing loss of fluid of low sodium concentration. It is important to appreciate that most body fluids contain less sodium than plasma and ECF.

Decreasing in water intake

It may be seen postoperatively, when oral fluid intake has ceased becausse of surgical necessity, or because the patient is unconscious, or has severe dysphagia or is old and feeble. When intake of water ceases, the insensible fluid loss from lungs and skin, and obligatory secretion of urine continues.

2. Water loss (hypotonic fluids), by:

- Skin (sweating)
- Lungs (hyperventilation)
- Gastrointestinal tract (aspiration of gastric juice, vomiting and diarrhea)
- Kidney (osmotic diuresis, diabetes insipidus, polyuric phase of chronic or acute renal failure)

Physiopathologic aspects

In predominant water depletion the concentration of sodium and chloride in the ECF and the osmotic pressure of the ECF gradually rise. If pituitary and renal function are normal this promotes the release of ADH which results in a small volume of concentrated urine. A fall in circulating blood volume stimulates aldosterone secretion causing maximal sodium retention and a low urinary sodium concentration. Volume depletion results in a falling glomerular filtration rate, but retention of nitrogenous products and a rise in the plasma urea occurs late, usually when the urinary flow falls below about 30 ml/h. If water depletion is accompanied by polyuria and a dilute urine, the loss is of renal origin. Effects tend to be more severe in infants and in old people because of poor renal compensating capacity, and in infants also because of relatively smaller fluid reserves.

The primary loss of water from the ECF is replaced from the ICF to maintain, as far as possible, the osmotic pressure of the plasma and tissue fluid. The concentrations of the ions in the plasma rise because there is a lag in water adjustment. The osmotic pressure of the ICF rises.

As replacement of the ECF is not complete, there is a sustained fall in the plasma volume, and slowly progressive hemoconcentration and circulatory changes.

II.1.3. Hypotonic extracellular fluid depletion

The syndrome of predominant sodium depletion develops most commonly when there is general loss of both water and sodium is replaced only by water or solutions of low sodium content.

Sodium loss

- renal (chronic renal failure, salt-wasting tubular disease, diuretics)
- endocrine (adrenal deficiency, hypoaldosteronism)
- water and sodium is replaced only by water or solutions of low sodium content.

Sodium sequestration

It includes inflammations, burns, intestinal occlusion, rapid accumulation of ascites

Sick-cell syndrome

It is part of many severe chronic illnesses, and is due to failure of the sodium pump. Sodium passes into the cells (which loose potassium and other intracellular ions) and the plasma sodium concentrations falls, but the total body sodium is unaltered.

Pathophysiologic aspects

When sodium containing fluids are lost from the body the ECF becomes hypotonic and some water passes into the more hypertonic ICF. The fall in tissue fluid osmotic pressure switches off ADH secretion and water is lost in the urine until the osmotic pressure of the ECF is restored. Water and sodium are thus "lost" in parallel and the ECF and plasma volumes fall, stimulating aldosterone secretion. In the presence of normal renal function, sodium is reabsorbed from the urine which contains less than 10 mmol/l. Typically, plasma sodium and chloride levels do not fall until 10 per cent of the ECF volume has been lost and ADH is secreted in response to volume depletion. The decrease in circulating blood volume and the decrease in glomerular filtration rate usually result in a slightly raised plasma urea at this point. The decreased GFR and secretion of ADH can result in a fall in urine volume.

Table no. 5. Clinical features of water depletion

Decreased interstitial volume
- reduced skin turgor
- slow rate of return of skin to original position when it raised between the examiner's fingers
- oral mucous membranes may be dry and axillary sweating decreased
Plasma volume depletion
- hypotension
- tachycardia
- the patient is lethargic, weak, confused
- oliguria
Laboratory findings (in plasma)
- increased hematocrit
- increased protein
- sodium (increased/normal/deecreased)
- increased creatinine
- increased blood urea nitrogen

II.2. WATER AND SODIUM EXCESS

II.2.1. Isotonic extracellular fluid expansion

There are a number of conditions in which adrenocortical hormone secretion is chronically increased.

1. *Decreased renal perfusion*: renal artery stenosis, malignant hypertension, essential hypertension, cardiac failure
2. *Edematous states*, with increased plasma volume: increased hydrostatic pressure (cardiac failure), decreased oncotic pressure (malnutrition, nephrotic syndrome, cirrhosis), increases in capillary permeability, or decreased lymphatic uptake.
3. *Increased mineralocorticoid secretion*: Conn's syndrome and Cushing's syndrome.

Pathophysiologic aspects

Decreased renal perfusion may result in stimulation of urine and aldosterone secretion causing secondary aldosteronism.

This results in sodium reabsorption and consequently water retention as a result of the increasing ECF osmolality stimulating ADH secretion; the ECF volume is expanded.

Continuing sodium retention does not occur, probably due to sodium excretion caused by natriuretic hormones and the plasma sodium level is therefore usually on the upper limit of the normal.

Volume expansion causes hypertension and edema.

II.2.2. Hypertonic extracellular fluid expansion

1. *Excess sodium intake*: by drinking sea water or by iatrogenic sodium excess (hypertonic bicarbonate)
2. *Decreased sodium excretion*: chronic renal failure, hyperaldosteronism, Ccushing's syndrome, glucosteroids therapy
3. *Edematous states in the conditions of restrained water intake* (congestive heart failure, cirrhosis, nephrotic syndrome)

Pathophysiologic aspects

Predominant sodium excess is only important if water is unavailable. It invariably gives rise to hyperosmolality of the ECF with thirst and mental confusion, coma and death due to cerebral dehydration. This is because the increasing ECF osmolality results in water leaving the cells and increasing the volume of the ECF. This results in plasma volume expansion, aldosterone is switched off and sodium is lost in the urine. At the same time the high osmolality resukts in maximum ADH secretion, the urine is therefore concentrated and of high sodium content.

II.2.3. Hypotonic extracellular fluid expansion

Water excess can only occur if normal homeostatic mechanisms have failed or, occasionally, if they are overriden.

1. *Renal disease*: acute renal failure, chronic renal failure
2. *Congestive heart disease, cirrhosis*

3. *Inappropriate secretion of antidiuretic hormone*: head injury, intracranial hemorrhage, encephalitis, tumours which secrete ADH-like peptides, severe illness).
4. *Psychogenic polydipsia*

Pathophysiologic aspects

ECF volume expansion may result in cardiac failure if the heart is already compromised and occasionally edema is seen. If hypoosmolality has developed rapidly, cerebral edema may lead to anorexia, lethargy, confusion and coma. In the presence of normal renal function the increase in plasma volume and renal perfusion results in decreased aldosterone secretion with increased urinary loss.

Clinical features of water excess

ECF volume expansion may result in cardiac failure if the heart is already compromised and occasionally edema is seen.

DISTURBANCES OF SODIUM METABOLISM

I. Hypernatremia

Hypernatremia is an increase in serum sodium concentration above the reference range of 135-145 mmol/l.

Causes of hypernatremia

1. water depletion
2. water and sodium depletion
3. excessive sodium intake or retention in the ECF

Water depletion

1. *Decreased intake*: a decreased water intake over a period of time when insensible losses have continued leads to decreased ECF and ICF volumes. The total sodium content of the ECF is unchanged. This is the most common reason for hypernatremia. A frequently encountered example is the elderly person who becomes ill and is unable to get something to drink.
2. *Water loss*: diabetes insipidus: impaired ADH secretion; nephrogenic diabetes insipidus: renal tubular cells do not respond to the ADH

Water and sodium depletion

Hypernatremia will occur only if more water than sodium is lost.

1. renal loss: osmotic diuresis (diabetes mellitus)
2. gastrointestinal loss: diarrhea, vomiting, especially in children
4. skin loss: excessive sweating

Increase in sodium content of the ECF

1. excessive sodium intake : administration of sodium in bicarbonate for the correction of an acidosis
2. increased sodium retention:- primary hyperaldosteronism (Conn's syndrome)
- Cushing's syndrome

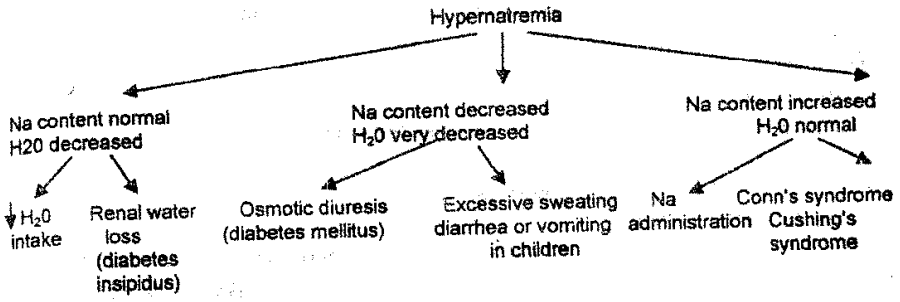


Figure no. 14
Etiology of hypernatremia

Clinical features

Consequences of ECF volume disturbances

The clinical features associated with the hypernatremic patient are available. If there have been fluid loss then the features of dehydration may be present. In the case of salt gain, there may be indications of fluid overload such as raised jugular venous pressure and pulmonary edema.

Consequences of cellular dehydration

The principal manifestations of hypernatremia are observed in the central nervous system. Confusion, and increased neuromuscular iritability appear to be due to dehydratation of brain cells.

II. Hyponatremia

Hyponatremia is a significant fall in serum sodium concentration below the reference range of 135-145 mmol/i.

Causes

1. Retention of water
2. Loss of sodium

1. Retention of water

If fluid loss is not apparent from clinical hystory, the reason for hyponatremia is usually water retention.

Hyponatremia due to water overload without a decrease in total body sodium is the commonest biochemical disturbances encountered in clinical practice. Further considerations of hyponatremia of this type depends on whether patient has edema or not. Edema is rapidly diagnosed by looking for pitting in the lower extremities of ambulant patient or in the sacral area of recumbent patients.

Non-edematous hyponatremia

Patients with non-edematous hyponatremia have a normal total body sodium and exhibit the features of the so-called syndrome of inappropriate antidiuresis (SIAD).

This syndrome is encountered in many conditions:

- infections (e.g. pneumonia)
- malignancy (e.g. carcinoma of the bowel or the lung)
- trauma (e.g. abdomonal surgery)
- drug - induced (e.g. thiazide diuretics)

Pathophysiologic aspects

Patients suffering from any of the above have non-osmotic AVP stimulation and, if they are exposed to excessive water loods, in the form of oral drinks or intravenous glucose solutions, they will become hyponatremic .

The non specific regulation of AVP overrides the osmotic regulatory mechanism and this result in water retention which is a non-specific feature of illness. This is illustrated by the finding that only 4% of the healthy population have a serum sodium concentration less than 138 mmol/l, more than 40% of inpatients have hyponatremia to this extent.

AVP has other effects in the body aside from regulating renal water handling.

Actions of AVP, other than renal water regulation

- Potent vasoconstrictor
- Potent hormonal stimulator of hepatic glycogenolysis
- Increases the plasma concentration of factor VIII-hence the use of the AVP analogue DDAVP in mild hemophilia
- Augments ACTH secretion from the anterior pituitary thus increasing cortisol production

Clinical features

The patients are hyponatremic, normotensive, have a normal glomerular filtration and a normal serum urea and creatinine concentration. Their urine flow rate is usually less than 1,5l/day.

Edematous hyponatremia

Patients who have generalized edema have an increase in both total body sodium and water. The main causes of edema are heart failure and hypoalbuminemia, and in both these conditions patients have a reduced effective blood volume.

Heart failure	The effective blood volume is reduced because the pumping action of the heart is unable to maintain a satisfactory circulation of the blood and ECF.
Hypo-albuminemia	The effective blood volume is reduced because the hypoalbuminemia lowers the plasma oncotic pressure. This disrupts the normal excahnge of solute and fluid in the capillary bed resulting in unsatisfactory circulation of the blood and ECF. Hypoalbuminemia occurs when synthesis is inadequate due to liver disease or when losses exceed the liver's synthetic capacity as occurs in the nephrotic syndrome.

Pathophysiologic aspects

In response to the reduced effective blood volume, aldosterone is secreted and causes sodium retention to allow the ECF volume to expand. The reduction in the effective blood volume is one of the non-osmotic stimuli for ADH secretion and consequently water is retained. The retention of relatively more water than sodium in the ECF results in hyponatremia.

Sodium loss

Although hyponatremia commonly results from water retention, it may also be associated with sodium depletion. This occurs only if there is pathological sodium loss. Such losses may be from the gastrointestinal tract or in urine.

Gastrointestinal losses: vomiting, diarrhea, fistula.

Urinary losses: aldosterone deficiency (Addison; syndrome); drugs which antagonize aldosterone action ssuch as spironolactone

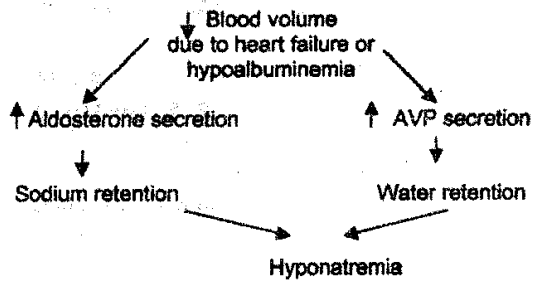


Figure no. 15
Pathogeny of edematous hyponatremia

Pathophysiological aspects

Initially in all of the above, sodium loss is accompanied by water loss and serum sodium concentrations remains normal. As sodium loss proceeds, the reduction in ECF and blood volume stimulates arginine vasopressin secretion. Remember that the non-osmotic control of AVP secretion overrides the osmotic control mechanism. The increased AVP secretion causes water retention and thus patients become

hyponatremic. Also, patients become hyponatremic because a deficit of isotonic sodium containing fluid is replaced only by water, either orally intravenously.

Clinical features

Consequences of cellular water expansion

Neurologic dysfunction is the principal clinical manifestations of hyponatremia. It is due to intracellular movement of water, leading to swelling of brain cells. Patients may be lethargic, confused, stuporous or comatose.

Disturbances of potassium metabolism

I. PHYSIOLOGY

The body contains about 3400 mmol of potassium, of which only 60 mmol (about 2%) are extracellular. The small fraction of the total boddy potassium which is in the extracellular compartment is distributed porportionatelly between the interstitial and plasma spaces. The concentrations in serum is around 45 mmol/l.

1.1. External balance of potassium

The external balance of potassium depends principally on dietary intake and renal excretion. only in seveere diarrrhea does fecal loss become a significant route of potassium loss.

Kidneys respond to the variations in dietary intake of potassium by modyfying secretion of potassium by the distal tubule. This is regulated by aldosterone and by the rate of sodium delivery to the distal tubules, but there is also a passive component.

1.2. Internal balance of potassium

Whereas serum potassium concentrations do not vary apprreciably in response to water loss or retention. factors which cause even a small or sudden shift of intracellular potassium will cause a big change in the ECF potassium content and concentration.

Insulin	The cell membrane Na/K ATP-ase actively transfer potassium into cells while sodium is pumped out, an activity which is stimulated by insulin.
Hydrogen ions	Many hydrogen ions are buffered inside cells. As the concentration of hydrogen ions increases with the development of acidosis, potassium ions are displaced from the cell in order to maintain electroneutrality. The opposite can occur in a metabolic alkalosis. These hydrogen ions changes cause marked alterations in serum potassium concentration.

1.3. Role of potassium

Despite its low concentration in the ECF, potassium determines the resting membrane potential of cells. Changes in potassium concentration mean that

"excitable" cells , such as nerve and muscle, may respond differently to stimuli. In particular, because the heart is largely muscle and nerve, too high or too low plasma potassium concentration may have life-threatening consequences.

II. Hyperkalemia

Hyperkalemia is the commonest and most serious electrolyte emergency encountered in clinical practice.

Causes:

1. *Excessive intake*: miscalculated therapeutic intravenous injection or, rarely, by consumption of large volume of fruit juice.
2. *Reduced renal loss*:
- fall in glomerular filtration rate: acute and chronic renal failure
- reduced tubular secretion (Addison's disease)

3. *Shifts between extracellular and intracellular spaces*
- acidosis
- cell damage: hemolysis, trauma, burns, tumour cell necrosis
- diabetic hyperkalemia

Clinical effects of hyperkalemia

Hyperkalemia lowers cell membrane potential and causes increased cardiac excitability. The cardiac signs are heralded by the development of tall and peaked T-waves on the ECG. Above 7.0 mmol/l there is a serious risk of cardiac arrest. Hyperkalemia causes muscle weakneess which may be preceded by paresthesiae.

III. Hypokalemia

The causes of hypokalemia include:

1. *excess renal loss*
- mineralocorticoid excess
- diuresis: diuretics and osmotic diuresis
- metabolic alkalosis
- renal tubular acidosis
- drug induced (thiazide diuretics)

2. *gastrointestinal loss*
- vomiting
- diarrhea
- K-secreting villous adenomas

3. *shifts between extracellular and intracellular spaces*
- acute alkalosis
- insulin therapy
- hypokalemic periodic paralysis

Clinical effects of hypokalemia

The main clinical effects are: severe weakness, hyporeflexia and cardiac arrhytmias.

Abnormalities in the ECG are common. The characteristic changes include flattening and inversion of the T-wave and increased prominence of the U-wave.

I.10. PATHOPHYSIOLOGY OF ACID AND BASE BALANCE

Acids are produced continuously during normal metabolism. Despite the addition of a great amount of carbonic acid and non-volatile acids to the body fluids daily, the free hydrogen ion concentration of these fluids is normally between 7.35-7.45. The pH of the intracellular fluids cannot be determined with precision, but most methods suggest a mean intracellular pH in the range of 6.9.

Regulation of acid-base balance

It involves the following:
I. Buffer systems
II. Lung
III. Kidney

I. BUFFER SYSTEMS

Immediate defense against untoward damages in pH is provided by buffers than can take up or release protons instantaneously in response to changes in acidity of body fluids.

The principal buffers in the blood are:
1. bicarbonate-carbonic acid ($NaHCO_3$ / H_2CO_3);
e.g. $HCO_3 - (NaHCO_3) + H^+(HCl) \longrightarrow H_2CO_3 (+NaCl)$
2. monosodic phosphate-disodic phosphate NaH_2PO_4 / Na_2HPO_4
3. protein – proteinate
4. hemoglobin / reduced hemoglobin

Within the cell the most important buffers are:
- bicarbonate

- proteins
- organic phosphates.

Because intracellular and extracellular buffers are functionally linked, measurement of the plasma bicarbonate system provides useful information about total body buffers. The relationship among the elements of the bicarbonate system is usually described in terms of the Henderson-Hasselbach equation:

$pH = pK + \log([HCO_3^-] / [H_2CO_3])$

This equation suggests that the pH depends on the metabolic factors (HCO_3^-) and respiratory factors (H_2CO_3). Normally, the ratio bicarbonate to carbonic acid is:

$HCO_3^- / H_2CO_3 = (27 \text{ mEq/l}) / (1.356 \text{ mEq / l}) = 20/1.$

II. ROLE OF THE LUNG

The principal acid product of metabolism is carbon dioxide, eqeuivalent to potential carbonic acid. The normal concentration of carbon dioxide in body fluids is $pCO_2 = 40$ mm Hg and this value is fixed by the lungs. The increase in arterial carbon dioxide partial pressure leads to decrease of pH and to the stimulation of respiratory center. The increase in ventilation rate allows to eliminate the carbonic dioxide excess.

III. ROLE OF THE KIDNEYS

The main source of non-volatile acids is the metabolism of methionine and cystine in diatery proteins, which produces sulfuric acid. The normal rate of production of non-volatile acids would be sufficient to deplete the body buffers completely in 10 to 20 days, were it not for the ability of the kidney to eliminate protons from the body by secretion into the urine, thereby regenerating bicarbonate and cell buffer capacity.

The main functions of the kidney in acid-base balance can be viewed as:
1. Retention of extracellular bicarbonate;
2. Excretion of protons of non-volatile acids produced by metabolic processes.

ACID-BASE DISORDERS

In practice, classification of acid-base disorders is based on measurements of changes in the bicarbonate-carbonic acid system.

$$HCO_3^- / H_2CO_3 \begin{cases} \uparrow (>20) = \text{alkalosis} \\ \downarrow (<20) = \text{acidosis} \end{cases}$$

Alkalosis
- metabolic ↑ HCO_3-
- respiratory ↓ pCO_2

Acidosis
- metabolic ↓ HCO_3-
- respiratory ↑ pCO_2

Table no. 6. Acid-base disorders

Acid-base disorder	Cause	Bicarbonate-carbonic acid ratio (normally: 20:1)	Compensation
Respiratory acidosis	Hypoventilation (retained CO_2)	Ratio <20/1	Renal: retention of HCO_3-; excretion of acid salts; increased ammonia formation
Respiratory alkalosis	Hyperventilation (excessive loss of CO_2)	Ratio >20/1	Renal: retention of HCO_3-; excretion of acid salts; increased ammonia formation
Metabolic acidosis	Retention of fixed acids Loss of base bicarbonates	Ratio <20/1	Lungs: hyperventilation Renal: as in respiratory acidosis
Metabolic alkalosis	Loss of fixed acids Gain of base bicarbonate K^+ depletion	Ratio >20/1	Lungs: hypoventilation Renal: as in respiratory alkalosis

ACIDOSIS

It is defined as a disturbance which tends to add acid or to remove alkali from body fluids.

I. Metabolic acidosis

The causes of metabolic acidosis are commonly divided into two groups according to whether the anion gap is normal or increased. The anion gap is calculated by substracting the sum of the plasma concentrations of Cl^- and HCO_3 from the Na^+ concentration. The normal value 12.

140 mEq / l – (104 mEq / l + 24 mEq / l) – 12 mEq / l = normal anion gap

Rather, the anion gap represents unmeasured anions because the sum of the plasma chloride + bicarbonate concentrations is less than the serum sodium concentration.

The cause of high anion gap metabolic acidosis is an increase in unmeasured anions such as sulphate, phosphate, lactate and other organic acids. If the acidosis is caused by loss of bicarbonate (such as diarrhea) or gain of chloride acid (for example administration of ammonium chloride), the anion gap will be normal. Conversely, if

the acidosis is due to increased production of an organic acid (such as lactate acid in circulatory shock) or the retention of sulfuric or phosphate acid (for example in renal failure), the concentration of unmeasured anions (anion gap) increases.

Causes

1. Increased anion gap

A. Increased acid production
- a. ketoacidosis (diabetic, alcoholic)
- b. lactic acidosis
  - secondary to circulatory or respiratory failure
  - associated with various disorders (leukemia, lymphoma, tumours)
  - drugs and toxins
  - enzyme defects
- c. poisoning (salicylates, ethylene glycol, methanol)

B. Renal failure

2. Normal anion gap

A. Renal tubular dysfunction
- a. renal tubular acidosis
- b. hypoaldosteronism
- c. "potassium sparing" diuretics

B. Loss of alkali
- a. diarrhea
- b. uretero-sigmoidectomy
- c. carbonic anhydrase inhibitors

C. Production of HCl (ammonium chloride cationic aminoacids)

There are three basic mechanisms of metabolic acidosis:
- a. Increased production of non-volatile acids
- b. Decreased acid excretion by the kidney
- c. Loss of alkali

Extracellular bicarbonate is reduced by reaction with hydrogen ions or, in patients wasting alkali, by loss of bicarbonate in urine or stool.

The decrease in pH stimulates respiration, and pCO_2 is lowered. When the kidney function is normal, net acid excretion increases promptly in response to metabolic acidosis. Most of the initial urine is due to increased filtration of urinary phosphate. Over several days, ammonia production by the kidney increases and becomes the most important mechanism for excreting excess proteins.

Clinical manifestations

Acute metabolic acidosis is usually caused by over production of non-volatile acid.

Chronic metabolic acidosis is most frequently due to renal dysfunction.

Diarrhea is a common cause of either acute or chronic acidosis.

In acute metabolic acidosis hyperventilation is usual and may be intense (Kussmaul's respiration). Acute, severe acidosis produces a variety of non-specific symptoms: fatigue, confusion, stupor, coma.

Chronic metabolic acidosis may produce no symptoms or may be associated with fatigue and anorexia.

II. Respiratory acidosis

Failure of ventilation promptly increases pCO_2 (carbonic acid) because metabolic production of CO_2 is so rapid. Acute respiratory acidosis is modulated to a limited degree by tissue buffers. If hypercapnia is sustained, renal acid excretion is enhanced and bicarbonate reabsorption is stimulated.

Causes of respiratory

1. Respiratory center supression:
- cerebral disease
- drugs
2. Ventilatory dysfunction: restrictive or obstructive type.

Clinical manifestations

It is often difficult to separate the manifestations of respiratory acidosis from those of associated hypoxia. Moderate hypercapnia has no specific clinical features. When pCO_2 exceeds 70 mm Hg, patients become progressively confused and obtunded. Papilledema may occur, apparently because intracranial pressure is increased by the cerebral vasodilatation characteristic of hypercapnia.

ALKALOSIS

I. Metabolic alkalosis

Metabolic alkalosis is usually initiated by increased loss of acid from the stomach or the kidney. However, excretion of bicarbonate at hogh plasma concentrations is normally so rapid that alkalosis will not be sustained unless bicarbonate reabsorption is enhanced or alkali is continuously generated at a great rate.

Clinically, maintenance of metabolic alkalosis is most often due to stimulation of bicarbonate reabsorption by a volume (chloride) deficit. During volume depletion, renal conservation of sodium takes precedence over other homeostatic mechanisms, such as correction of alkalosis. Since in alkalosis a large fraction of plasma sodium is paired with bicarbonate, complete reabsorption of filtered sodium required reabsorption of bicarbonate as well.

Causes of metabolic alkalosis

1. **Associated with volume (chloride) depletion**
a. **Vomiting or gastric drainage**
b. **Diuretic therapy**
c. **Posthypercapnic alkalosis**
2. **Associated with hyperadrenocorticism**
a. **Cushing's syndrome**
b. **Primary aldosteronism**
c. **Bartter's syndrome**
3. **Severe potassium depletion**
4. **Excessive alkali intake**
a. **Acute**
b. **Milk-alkali syndrome**

Clinical manifestations

There are no specific clinical signs or symptoms. Severe alkalosis may cause apathy, confusion and stupor. If serum calcium is bordeline or low, rapid development of alkalosis may lead to tetany. Plasma potassium concentration is often reduced and the EKG may reveal changes in T and U waves typical of hypokaliemia.

II. Respiratory alkalosis

Acute reduction in CO_2 concentration releases hydrogen ion from tissue buffers, which minimizes alkaliemia by reducing plasma bicarbonate. Acute alkalosis also diminishes glycolisis; increased production of lactic and pyruvic acids lower serum bicarbonate and raises plasma concentrations of the corresponding anions.

In chronic hypocapnia, plasma bicarbonate is further reduced because the decreased pCO_2 inhibits tubular reabsorption and generation of bicarbonate.

Causes of respiratory alkalosis

1. Hypoxia
   a. acute (pneumonia, asthma, pulmonary edema, hypotension);
   b. chronic (pulmonary fibrosis, cyanotic heart disease, high altitude anemia);
2. Respiratory center stimulation
   a. anxiety
   b. fever
   c. gram-negative sepsis
   d. salicylate intoxication
   e. cerebral disease (tumour, encephalitis)
   f. hepatic cirrhosis
   g. pregnancy

h. after correction of metabolic acidosis

3. Excessive mechanical ventilation

Clinical Manifestations

In acute respiratory alkalosis, the clinical is rather characteristic: patient complain of paresthesias, and tingling, of high-headness; and if alkalosis is sufficiently severe of manifestations of tetany.

Alkalosis directly enhances neuromuscular excitability; this effect, rather than the modest decrease in ionized plasma calcium induced by alkalosis, is probably the major cause of tetany.

Severe respiratory alkalosis may cause confusion or loss of consciousness perhaps due to cerebral vasospasm induced by hypocapnia.

I.11. PATHOPHYSIOLOGY OF SHOCK

Shock is a multifactorial condition occuring in a variety of syndroms that is characterised by a reduction in tissue perfusion and oxygen delivery below the levels required to meet normal metabolic demands; inadequacy of tissue perfusion is ordinarily accompanied by a decreased arterial blood pressure.

Shock, often loosely called *vascular collapse* may develop following any serious assault of the homeostasis of the body. In the final analysis, shock constitutes widespread hypoperfusion of cells and tissues due to reduction in the blood volume or cardiac output, or redistribution of blood resulting in a decrease of effective circulating volume. The reduced perfusion of cells and tissues if unchecked leads to irreversible injury and death of the cells, and eventually of the patient.

I. Ethiology and pathogenesis

Shock is a state in which the perfusion of body tissues is inadequate for normal metabolic demands. This decreased perfusion is generally the result of a decreased cardiac output resulting either from the inability of the heart to pump the normal venous return or from a decreased volume of blood secondary to a decreased venous return. These two mechanisms which lead to a decreased cardiac output, define two major types of shock: cardiogenic and hypovolemic shock (figure no. 16).

In cardiogenic shock due to myocardial infarction, myocarditis or pericardial tamponade, a depressed systolic cardiac function (ejection fraction less than 20%) is responsible for the decreased cardiac output and, consequently, for the shock symptoms. In hypovolemic shock, however, a decreased blood volume is reflected in a reduced venous return to the heart, which in turn leads to a decreased cardiac output. A reduction in blood volume results from either external or internal fluid loss. Hemorrhage, diarrhoea, excessive urine formation and perspiration are the major mechanisms of external fluid loss; internal fluid loss usually results from an increase in the permeability of the microvasculature caused by endotoxemia, burns, trauma or anaphylaxis.

In the case of burn or trauma, direct damage to microcirculation is the mechanism by which vascular permeability is increased. Immunologic mechanisms, coupled to the activation of the complement and the release of anaphylatoxins, increase vascular permeability in anaphylaxis.

Types of shock. Shock may be precipitated by any massive insult to the body, such as profuse hemorrhage, severe trauma or burns, extensive myocardial infarction, massive pulmonary embolism or uncontrolled bacterial sepsis. All these causes of the shock can be grouped into four categories presented in table 7.

Table 7: Classification of shock

Type of shock	Clinical examples	Principal mechanisms
1. Cardiogenic	Myocardial infarction, heart rupture, arrhytmias, cardiac tamponade, pulmonary embolism	Failure of the myocardial pump due to intrinsic myocardial damage or extrinsic pressure or obstruction to outflow
2. Hypovolemic	Hemorrhage, fluid loss (e.g. vomiting, diarrhoea, burns)	Inadequate blood or plasma volume
3. Septic	Overwhelming bacterial infections: gram negative (endotoxic shock) or gram positive septicemin	Peripheral vasodilation and pooling of blood; cell membrane injury, endothelial cell injury with DIC
4. Neurogenic	Anesthesia, spinal cord injury	Peripheral vasodilation with pooling of blood

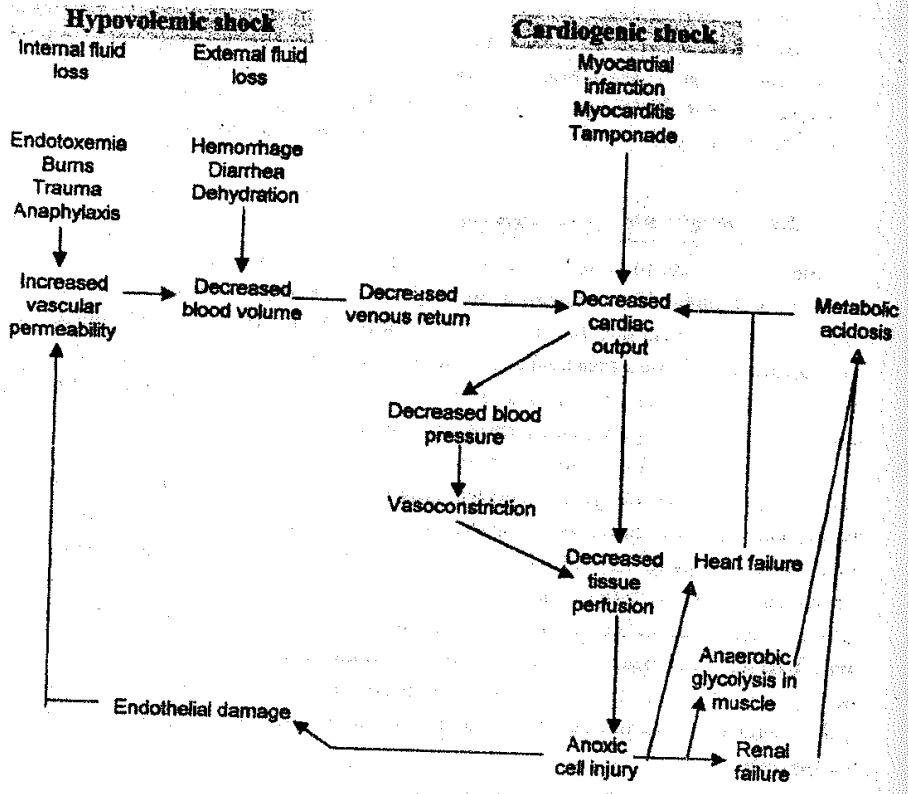


Figure no. 16

The pathogenesis of shock associates a large number of factors in its progression. It may be initiated by one of two main events: pump failure (cardiogenic shock); loss of circulatory volume (hypovolemic shock). Hypovolemic shock may result from either internal fluid loss (in endotoxemia, burns, trauma, anaphylaxis) or external fluid loss (hemorrhage, diarrhea, dehydration); in both instances there is decreased cardiac output and decreased tissue perfusion, resulting in an anoxic cell injury. Metabolic acidosis, occuring as a result of the renal failure and increased anaerobic glycolysis: heart failure; and endothelial damage further impair the cardiac output; in addition, the last event increases vascular permeability, decreasing effective blood volume.

A review of this table will indicate that the mechanisms underlying cardiogenic and hypovolemic shock are fairly obvious. As might be expected, they are associated with low cardiac output hypotension, impaired tissue perfusion and cellular hypoxia. The term shock encompasses all the hemodynamic reactions that may occur in response to such alterations of hemodynamic hemostasis.

Shock initiates compensatory mechanisms that, for a while, sustain the organism at borderline levels. If compensatory mechanisms exhausted, shock is said to enter on irreversible phase.

In the natural course of shock, a rapid circulatory collapse leads to impair cellular metabolism and death.

Shock is not synonymous with low blood pressure although hypotension is commonly a part of the shock syndrome. Hypotension is a late sign of shock and indicates failure of compensation. Blood flow is dependent on both perfusion pressure and vascular resistance. Peripheral flow may fall below critical levels, but extreme vasoconstriction can maintain central arterial blood pressure.

This distinction between shock and hypotension is of clinical relevance because rapid restauration of nutrient blood flow is a primary goal in treating shock. When blood pressure alone is raised following vasopresive drugs administration, nutrient blood flow may actually be diminished.

The effect of both events is decreased cardiac output and decreased tissue perfusion. The resulting anoxic cell sets into motion several vicious cycles.

Metabolic acidosis (renal failure, increased anaerobic glycolysis) and heart failure lead to a further decline in cardiac output.

Septic shock. Endotoxic shock is multifactorial; it is associated with vasodilation, decreased tissue perfusion, endothelial damage and direct cellular injury.

Endothelial damage increases vascular permeability and decreases effective blood volume, reducing venous return and decreasing cardiac output, aggravating anoxic cell injury.

The basis of septic shock is much more complex and still imperfectly understood. The majority of cases of septic shock are caused by endotoxin - producing gram negative bacilli - *Escherichia Colli, Klebsiella Pneumoniae, Pseudomonas Aeruginosa, Serratia, Bacteroides* and *Proteus* species - hence the term endotoxic shock. However, gram positive cocci such as pneumococci may produce a similar syndrome. In contrast to hypovolemic and cardiogenic shock, the cardiac output in septic shock is not low at the outset; however, the total peripheral resistance is inappropriately low, owing to arteriolar vasodilation. This results principally from release of vasoactive mediators such as complement components, but direct toxic injury to the vessels may also be involved (figure no. 17).

As a consequence, veins (the so-called capacitance vessels) become engorged with blood, producing peripheral pooling. The disproportion between the circulating blood volume and the expanded volume of the circulatory bed thus induces a state of relative hypovolemia and impaired perfusion results.

Sequestration of large volumes of blood in the capacitance vessels impairs venous return and leads eventually to low cardiac output. Endotoxins or other bacterial toxins also act on many other fronts: endotelial injury leads to activation of both intrinsic and extrinsic clotting pathways, leading to disseminated intravascular coagulation, which further aggravates tissue hypoxia. Activation of the complement generates many factors, including those that increase vascular permeability and attract neutrophils.

Accumulation of neutrophils in tissues, particularly the lung, followed by release of their enzymes and production of toxic free radicals, damges pulmonary epithelium and initiates the acute respiratory distress syndrome. Recent studies suggest that endotoxin-mediated activation of the mononuclear phagocyte system and the consequent release of TNF α is a key event in the pathogenesis of septic shock (figure no. 17). This cytokine signals the synthesis and release of secondary mediators, including prostaglandins and platelet-activating factors. TNF α also promotes intravascular coagulation and capillary thrombosis. Indeed, most of the metabolic and hemodynamic effects of endotoxins can be mimicked by the infusion of TNFα in laboratory animals. Conversely, antibodies directed against this cytokine can reverse experimentally induce septic shock. In addition to causing the release of biologically active mediators, bacterial toxins also cause direct injury to cells and tissues. Thus, even the cells that are well perfused fail to extract adequate oxygen from the blood. This results in a subnormal arteriovenous oxygen difference often noted in septic shock.

To summarise, septic shock is associated with distributive deffects (peripheral pooling), endotoxin-mediated activation of the inflammatory-immune response and direct toxic injury to cells and tissues. All of these acting in concert lead to failure of multiple organ system and in many cases death.

The lipopolysaccharide portion of bacterial endotoxins activates complement by two antibody-independent mechanisms. The lipid region of the lipopolysaccharide molecule (lipid-A) binds directly to C1 and initiates complement activation by the classical pathway. The polysaccharide portion of the molecule activates the alternative pathway by a mechanism that is independent of lipid-A. Complement activation generates potent chemotactic factors that cause leukocytes to marginate in the microcirculation, an event followed by degranulation and endothelial injury. The neutrophil has therefore been suggested as playing a central role in the pathogenesis of the endotoxin-associated injury. Oxygen radicals and neutrophil-derived proteases have, indeed, been implicated in neutrophil-mediated injury to the endotelium.

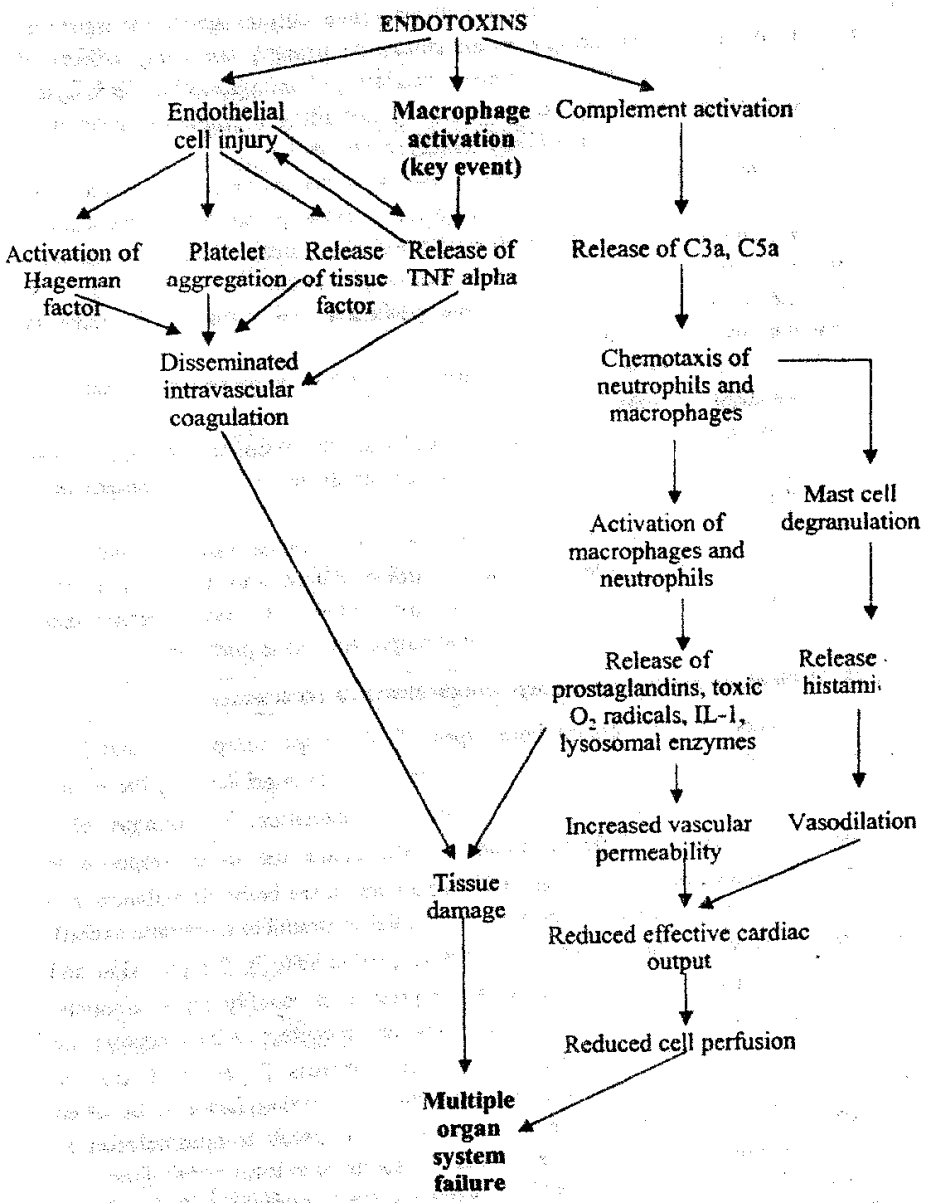


Figure no. 17
Pathogenesis of endotoxic shock

Alternatively, it has been suggested that endotoxin injures endothelial cells directly, and that activated complement and neutrophils only exagerate the injury by their interactions with the alterate endothelium. At present, the many effects of endotoxin on coagulation and complement, platelets, polymorphonuclear leukocytes, endothelial cells and macrophages/monocytes do not allow a simple explanation of the pathogenesis of microvascular injury initiates septic shock.

In both hypovolemic and cardiogenic shock, a decreased cardiac output and resultant decreased tissue perfusion make up the essential pathogenetic mechanisms in the progression from reversible to irreversible shock. Anoxic injury is a common cellular consequence of the initial decrease in tissue perfusion.

A vicious cycle of decreasing tissue perfusion and further cell injury is perpeutated by two mechanisms:

- injury to endothelial cells as a result of decreased tissue perfusion increases vascular permeability;
- In turn, the increased exudation of fluid from the circulation reduces blood volume, decreases venous return and further decreases cardiac output thus aggravating anoxic cell injury.

Decreased perfusion of the kidneys and skeletal muscles results in metabolic acidosis, which in turn further decreases cardiac output and tissue perfusion; decreased perfusion of the heart injures the myocardial cells and decreases their ability to pump blood, further reducing cardiac output and tissue perfusion.

II. Vascular compensatory mechanisms in shock

A. All blood vessels contain both types of adrenergic receptors α and β. In general, stimulation of α receptors results in constriction of arterioles, capillaries and veins, while stimulation of β receptors results in vasodilation. The number of α and β receptors varies in different blood vessels, hence the exact response to adrenergic receptors stimulation varies in different parts of the body. Stimulation of β receptors of the heart results in increase in myocardial contractility (inotropic action); β receptors predominate in the heart. α receptors predominate in the gut, skin and kidney. In the muscles, α and β receptors are present in roughly equal amounts. Generally, in the heart and brain, there are very few receptors. Alfa receptors are commonly innervated by the sympathetic system whereas β receptors are not innervated and respond to circulating cathecolamines. A further factor to be taken into account is a variable responsiveness of local blood vessels to accumulation of metabolites; the coronary circulation, e.g., is very responsive to local metabolites.

The capillaries are freely permeable to water and electrolytes.

Flow through capillaries is controlled by sphincter mechanisms at both ends, the pre- and post-capillary sphincters. The precapillary sphincters tend to open in

response to accumulation of local metabolites. The postcapillary sphincters respond to catecholamines both directly and via the sympathetic nervous system. Arise in catecholamines results in constriction of postcapillary sphncters. Control of capillaries is such that only one-third of all the capillaries is open in any one time. If all capillaries in the body are opened at the same time the capillary circulation could contain two to three times the circulating blood volume.

All types of shock are associated with a high level of circulating catecholamines. In the early stages this is beneficial and is responsible for maintaining the central blood pressure and allowing perfusion of privileged tissues, particularly the brain and heart. This is possible because the arterioles in the muscles skin and splanchnic beds are richly innervated with α receptors; the vessels of the brain and the vessels of the heart are poorly innervated with α receptors. As a result of sustained catecholamine production, the peripheral resistance increases.

Sustained catecholamine production causes further vein constriction which now acts as an obstruction to further venous return because catecholamines also constrict post-capillary sphincters, leading to capillary congestion and a further fall in venous return. Capillary congestion allows local metabolites of anaerobic metabolism to acumulate, leading to:

1. Precapillary sphincter relaxation and more capillary congestion
2. Opening of some of the two-thirds of the capillaries, which are normally closed at any one time, causing further pooling of blood, direct shunting from the arterial to the venous side and by-passing of the microcirculation. These changes further decrease venous return and tissue perfusion.
3. Increased capillary permeability and loss of intravascular fluid into the extracellular compartment.
4. Further cell damage causing release of vasoactive substances (histamine, 5-hydroxytryptamine and kinins) and resulting in further pooling in the microcirculation.

B. Feed-back mechanisms maintain blood flow to the vital organs, the heart and the brain, shifting it away from the periphery, skeletal muscle, skin, splanchnic bed, adipous tissue, limbs and some parenchymal organs. The compensatory mechanisms involve a. the sympathetic nervous system; b. the release of endogenous vasoconstrictors and hormonal substances; c. the local vasoregulation.

The integrated regulatory response increases cardiac output by increasing the heart rate and myocardial contractility while constricting the arteries and arterioles.

a. The increased sympathetic discharge also increases adrenal cathecolamine synthesis and the release of cathecolamines by the adrenal medulla. The skeletal muscle, splanchnic bed and skin arterioles respond to this increased sympathetic discharge while the cardiac and cerebral arterioles are less reactive. In this manner,

the increased sympathetic tone affects volume regulation. The marked arteriolar vasoconstriction results in reduced capillary hydrostatic pressure and in less fluid shifted into the interstitium, thus permitting an osmotic fluid shift from the interstitium to the vascular system. The sympathetic-adrenal response can completely compensate for a blood loss of 10% of intravascular volume. With a greater volume deficit, cardiac output and blood pressure can no longer be properly maintained and nutrient blood flow to tissues is reduced.

b. The renin-angiotensin-aldosterone mechanism also contributes to compensation. Renin converts the circulating angiotensiogen into angiotensin I, which is subsequently transformed to angiotensin II, the most potent endogenous vasoconstrictor. Angiotensin II also stimulates aldosterone secretion, which in turn stimulates sodium and water reabsorption, thus helping to maintain intravascular volume. A similar water-preserving action is provided by the pituitary antidiuretic hormone.

c. Vascular autoregulation preserves regional blood flow to vital organs, particularly the heart and the brain by vasodilation of the coronary and cerebral circulations in response to hypoxia and acidosis. The peripheral circulation of organs such as skin and skeletal muscles, which are less sensitive to hypoxia, do not display such a tightly controlled autoregulation.

III. Evolution of shock

Shock is a progressive disorder that, if uncorrected, may lead to death. Unless the insult is massive and rapidly lethal (e.g. a massive hemorrhage from a ruptured aortic aneurysm or an extensive infarction affecting the left ventricle), shock tends to evolve through two stages (figure no. 18):

I. Reversible
II. Irreversible

I. **Reversible** stages with two phases:

a. Initial non-progressive phase during which reflex vascular compensatory mechanisms are activated in response to the initial insult and perfusion of vital organs is preserved.

- Decreased tension on the stretch receptors (baroreceptors located in the aortic arch and carotid sinuses) stimulates the autonomic nervous system
- Renin-angiotensin-aldosterone system is activated in response to low renal perfusion
- Clinical manifestations during this initial phase include:
  - The person is awake but anxious; may complain of thirst
  - Skin: pale, moist and cool

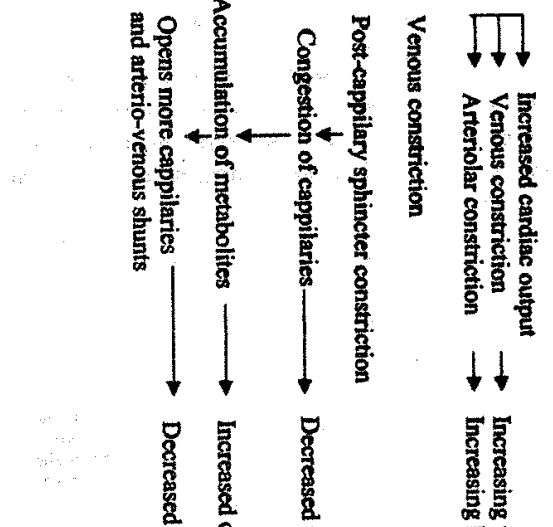


Figure 18
The pathophysiology of shock, reversible stage

- Lungs: tachypnea
- Heart: tachycardia, normotension
- Renal: decreased urinary output due to decreaed renal perfusion and ADH and aldosterone action

➢ Course: usually either resolves in a few hours or progresses

b. A **progressive phase** characterised by tissue hypoperfusion and onset of an ever-widening cycle of circulatory and metabolic imbalances. Uncompensated shock in which compensatory mechanisms fall to restore blood volume and tissue perfusion.leading to a deterioration in the clinical picture.

➢ Clinical features of this phase include:

- General manifestations-progressive alteration of the conscience
- Skin: cold and moist
- Lungs: tachypnea, dyspnea
- Heart: progressive bradycardia, drop in arterial tesion, acute pulmonary oedema with increased central venous pressure and increased pulmonary arterial pressure
- Urinary: oliguria

II. Finally, **an irreversible stage** that sets in after the body has incurred cellular and tissue injury so severe that even if therapy corrects the hemodynamic defect survival is not possible. Admittedly, these stages are somewhat arbitrary but a brief discussion of this sequence will severe to integrate the sequencial pathophysiologic and clinical alterations in shock.

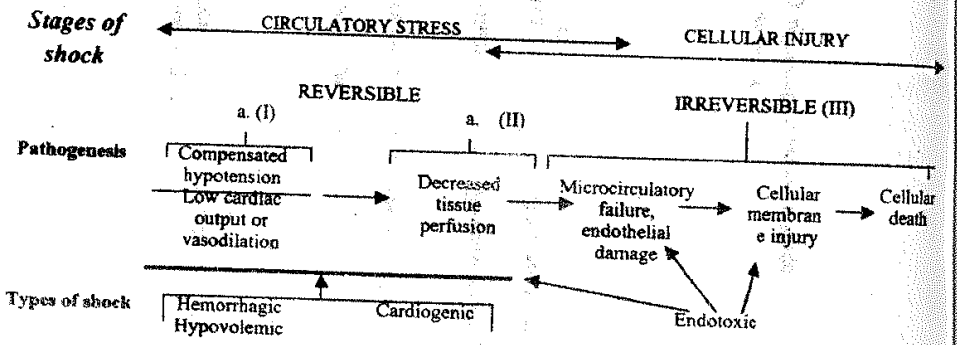


Figure no. 19

Pathogenesis and stages of shock. Stage I is non-progressive, stage II is progressive, and stage III is irreversible. Note that endotoxic shock is multifactorial; it is associated with vasodilation, decreased tissue perfusion, endothelial damage, and direct cellular injury.

During early shock (say, following blood loss) a variety of neurohumoral mechanisms come into play to maintain cardiac output and blood pressure. These

include the baroreceptor reflexes, release of cathecolamines, activation of the renin-angiotensin axis, antidiuretic hormone release and generalised sympathetic stimulation. The effect of all these are to produce tachycardia, peripheral vasoconstriction and conservation of fluid by the kidney. The vasoconstrictor response results in coldness and pallor of the skin. Since coronary and cerebral vessels are less affected by the sympathetic response, their calibre is not significantly affected and thus oxygen continues to be delivered to these organs. Obviously, therapetic manoeuvres have the best chance of success at this stage. Uncorrected, shock passes inperceptibly to the progressive phase during which the vital organs begin to experience significant hypoxia. With persistent oxygan deficit there is impairment of intracellular aerobic respiration, followed by anaerobic glycolysis and excessive production of lactate, which often induces metabolic lactic acidosis. The lowering of pH in the tissues obtrudes the vasomotor response; arterioles dilate and blood begins to pool in the microcirculation. Peripheral pooling not only worthens the cardiac output; it also favours anoxic injury to endothelial cells, thereby setting the stage for DIC. Release of TxA2, a potent platelet aggregator, has also been implicated in the occlusion of microvasculature. With widespread tissue hypoxia, the function of vital organs begins to deteriorate; often, the patient is confused and the urinary output begins to fall.

At some point in the downward spiral there is a transition from the reversible to irreversible stage. Widespread cell injury allows leakage of lysosomal enzymes that further aggravate shock state.

Lysosomal-mediated mechanisms (figure 20). Many of the cardiovascular, cellular and biochemical alterations that occur during shock can be explained by four major lysosomal-mediated mechanisms.

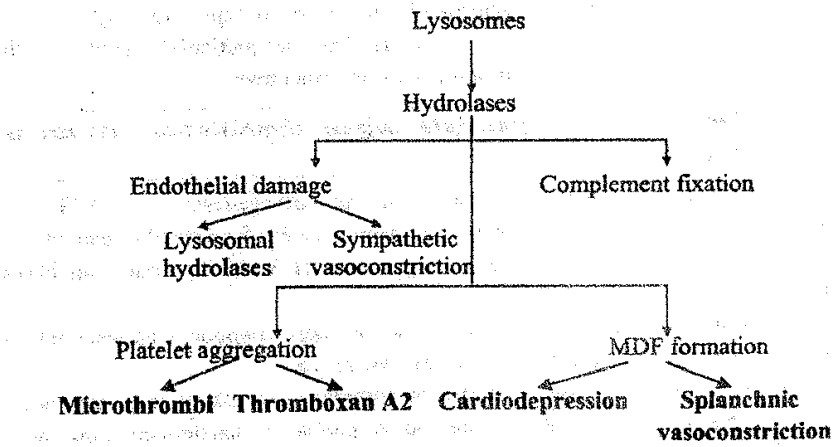


Figure no. 20

Lysosomal mediated mechanisms

1. Endothelial damage. First, lysosomal hydrolases, released into the systemic circulation, produce endothelial damage to the microvasculature of the lungs and other vital organs and cause fluid loss which leads to sympathetically mediated vasoconstriction and impaired uptake, transport and utilisation of oxygen.
2. Activation of complement. Second, certain lysosomal proteases participate in complement fixation which leads to the generation of protein fragments, some of which exert vasoonstrictor effects.
3. Platelet aggregation-microthrombi. Third, lysosomal hydrolases enhance platelet aggregation leading to formation of microthrombi which block flow in small vessels, especially in the liver, lungs, kidneys and heart. In addition, platelet aggregates release thromboxane A2 (TxA2), o potent vasoconstrictor agent.
4. Formation of myocardial depressant factor (MDF). Finally, lysosomal proteases lead to the formation of MDF which directly constricts the splanchnic vasculatureand causes cardiodepression.

The ischemic pancreas is believed to liberate a myocardial depressant factor (MDF), worthening the already poor cardiac performance.

Endotoxic shock may be surimposed on hypovolemic or cardiogenic shock if the ischaemic intestinal mucosa allows intestinal flora to enter the circulation. By this stage the patient has complete renal shut-down due to acute tubular necrosis.

Shock is associated with a number of specific changes in organs. The cellular and tissue changes induced by shock are essentially those of hypoxic injury; only their distribution is somewhat distinctive.

Late stages of shock are characterised by failure of multiple organ systems and hence cellular changes may appear in any tissue. They are particularly evident in the brain, heart, lungs, kidneys, adrenals and gastro-intestinal tract.

IV. Mechanisms of multiple organ dysfunction syndrome (MODS)

The molecular mechansims involved in the pathogenesis of MODS have remained illusive and continue to represent a major problem for critical ill patients.

MODS is currently one of the leading causes of morbidity following burns, trauma and sepis.

Acute lung injury and ARDS are by far the most common manifestations of organ dysfunction affecting over 150.000 per year in U.S.

The insults tipically result in release of numerous circulatory proinflammatory mediators (TNF alpha, interleukins, eicosanoids, proteases, platelet-activating factor and oxydant-generating enzymes) from the injured tissue and often involve other one or more remote tissues.

These proinflammatory mediators are released locally as part of a complex defense mechanism to help promote wound healing and combat foreign organisms or antigens.

To ensure that the proinflammatory mediators are not destructive, a series of antiinflammatory mediators (soluble TNF receptor, IL1 receptor antagonist and transforming growth factors) are also released.

When the insult is sufficiently severe, that local release of mediators results in an uncontrolled systemic inflammatory response consisting of:

- activation of inflammatory cells (neutrophils and macrophages)
- excess production of oxidants
- massive release of proinflammatory mediators into the systemic circulation

This cascade of events may be manifested as increased expression of adhesion molecules, increased margination, platelet adherence and reduced blood flow.

The secretion of proinflammatory mediators into the blood may also activate complement, which would further amplify the inflammatory cascade. These processes could be responsible for the pulmonary and cardiac injury associated with hepato-enteric syndrome which is characteristic of MODS.

The cellular and lysosomal derangements observed during shock not only explain the dysfunction observed within any one organ, but helps understanding multiple organ failure now recognised as a key feature of shock.

Clinicians are aware that shock is not merely the failure of one organ but is the progressive impairment of many key organs. The heart, liver, pancreas, lungs and kidneys are all involved at different stages in the pathogenesis of shock. For example:

- **The liver** is affected early and exhibits damage to the reticulo-endothelial system and cellular metabolism. Fatty change, severe perfusion deficits and sometimes central necrosis occur.
- **Pancreas** injury leads to impaired hormonal control of carbohydrate metabolism and also to formation of MDF.
- **Kidneys** may be severely affected in shock, resulting in oliguria, anuria, electrolyte disturbances and acid-base imbalance with acute tubular necrosis causing the accumulation of nitrogenous metabolites and toxaemia. Renal changes are commonly reffered to as acute tubular necrosis, but similar changes may be encountered in other settings.
- **Lungs** are seldom affected in pure hypovolemic shock because they are resistent to hypoxic injury, but when vascular collapse is caused by bacterial sepsis or trauma, changes may occur that is reffered to as *shock lungs*. The pulmonary lesions result from diffuse alveolar damage and give rise to acute respiratory distress syndrome, but these anatomic changes may be caused by a variety of clinical derangements. The damage to the lung causes diminished

exchange of oxygen and carbon dioxide, and impaired regulation of circulating humoral substances such as prostaglandins.

- **Adrenal** alterations encountered in shock comprise in essence that common to all forms of stress and so might be reffered to as *the stress response*. Early, there is focal depletion of lipids in the cortical cells beggining in the *zona reticularis* and then spreading progressively outward into the *zona fasciculata*. This loss of corticolipids implies not adrenal exhaustion but rather reversion of the relatively inactive vacuolated cells to metabolically active cells that utilise stored lipids for the synthesis of steroids.
- **The gastro-intestinal tract** may suffer patchy mucosal hemorrhages and necrosis refferd to as *hemorrhagic enteropathy*.
- Finally, **cardiac function** is impaired which leads to the collapse of the circulatory system and inadequate perfusion of the vital organs. The heart may undergo a variety of changes. Extensive lesions such as myocardial infarction or myocardial disease may of course be present. In addition, subendocardial hemorrhages and necrosis or zonal lesions sometimes appear in all forms of shock. The term *zonal lesion* reffers to apparent hypercontraction of a myocyte inducing shortening and scalloping of the sarcomere, fragmentation of the Z-band, distortion of the myofilaments and displacement of the mitochondria away from the intercalated disc. Subendocardial hemorrhage and zonal lesion are not diagnostic of shock and may be seen following administration of catecholamines or after prolonged use of the heart-lung bypass pump in cardiac surgery.
- **The brain** may develop so-called ischaemic encephalopathy.

Virtually all of these organ changes may revert to normal if the patient survives. However, loss os neurons from the brain and loss of cardiac myocytes are of course irreversible. Moreover, persitent pulmonary septal oedema may be converted into septal fibrosis, which is irreversible. However, most patients who suffer shock so severe as to produce irreversible changes succumb before these alterations become well developed.

Early vigurous administration of glucocorticoids such as methylprednisolone (30 mg/kg) may prevent these deleterious effects in vital organs by stabilizing cellular and lysosomal membranes.

In closing, one may ask when does shock becomes irreversible? Some would argue that if the initiating cause is removed, shock is reversible at any stage. The issue is moot but one fact is not: death from shock, despite the heroic measures by modern intensive care units, is still an everyday happening.

I.12. PATHOPHYSIOLOGY OF NEOPLASIA

The term "cancer" evoked numerous definitions but the simplest one between all is that of disordered cellular homeostasis with loss of the normal growth controlling mechanisms.

Literally, neoplasia means new growth: tumoral mass originating from the proliferation of an undifferentiatied cell, with embriological properties, without relation with chronobiological age of the organism.

1. Structural and metabolic differences between normal and malignant cells.

Cancer cells differ from normal cells in several ways:

a. Cancerous cell has a specific DNA modification (mutation, rupture of the chromosome) of a sensibile site in the genome called oncogene.

b. Loss of the responsiveness to normal growth controls, so that neoplastic cells continue to replicate in the absence of the stimulating growth factors (this is due to the ability of the cancerous cells to be stimulated by the growth factors in an autocrine way).

c. Neoplastic cells behave as parasites and compete with normal cells for their metabolic needs.

d. Neoplasms also enjoy a certain degree of autonomy, and therefore depend upon local environment and host nutritional status. Thus, their autonomy is not complete.

Malignant tumours are reffered to as **cancers** derived from the Latin denomination of the crab - cancers extend like crabs. The term "malignant" implies that the tumour is able to invade and destroy adjacent structures and spread to distant sites - **metastasis** - to cause death.

Benign tumours are composed of well differenciated cells very closely ressembling their normal counterparts. Cancers are characterized by a wide range of parenchymal cell differentiation, from those well differentiated to that undifferenciated.

Literally, the term "anaplasia" means, "to form backward"; it implies dedifferentiation: loss of the structural and functional differentiation.

2. Etiology

Intimate cause of cancer, e. g. what causes cancerous cells to proliferate continuously, is still unknown. However, two classes of agents inducing cell proliferation and tumour formation have been defined.

A. Exogenous factors: - chemical carcinogens
- radiant energy
- biological factors

B. Endogenous factors: - genetic factors
- immunological factors

CHEMICAL CARCINOGENS

About 200 years ago, scrotal skin cancer in chimney sweeps was attributed, by the English surgeon Sir Percival Pott, too chronic exposure to soot. He revealed that soot contains several major chemical carcinogenes (including benzopyrene and methylcolantrene) only a few years later.

Most chemical carcinogenes damage DNA either directly or following metabolic activation within the liver. They may be classified as follows:

1. **Direct-acting agents.**
   a. Alkylating agents used in the treatment of some cancers because of their ability to determine fatal mutations which lead the cell to cellular death (apoptosis) or to other mutation resulting in skin cancers (ie, treatment of leukemia leads to a secondary cancer: skin cancer)
   b. Sodium arsenite provokes gastro-intestinal cancers.

These agents do not undergo metabolic conversion, e. g. cytotoxic drugs - they are administred to destroy neoplastic tissues but they may induce different cancers by alterating the DNA of normal cells: leukaemia and skin cancers.

2. **Indirect-acting agents**. (They should be metabolised in order to become active).

a. **Polycyclic hydrocarbures**. They may be found in fossile fuels and they are derived from:
   - combustion of organic substances
   - high temperature combustion of tobacco in cigarette smoking. The latter are involved in the onset of lung cancer.

Epoxides are the principal products that result from metabolisation of most hydrocarbons in the liver. They are able to form covalent bonds with compounds such as DNA, RNA and proteins.

b. **Benzidine** is an aromatic amine currently used to test occult blood in the stool.

c. Some of the **dyes** were developped to colour food-butter yellow to make margarine more exciting are involved in liver cancer

d. **Nitrosamines** are formed in the stomach from nitroso compounds and amines. The first may be commonly found or may be formed within stomach by bacterias. They are involved in the onset of the gastric carcinoma.

e. **Aflatoxin B1** is a natural agent produced by some strains of *Aspergillus*, a mold that grows on stored graines and nuts. Strong correlations between the

dietary level of this food contaminant and the incidence of hepato-cellular carcinoma may be established.

Chemical carcinogens: mechanisms of action. Almost all of the chemical carcinogens are defficient in electrons and form covalent bonds with DNA, provoking gene alterations inducing miscoding errors during transcription and replication so they are considered mutagens.

The carcinogenity of chemical agents may be enhanced by subsequent administration of substances known as **promoters**, such as phorbol esthers. It seems more likely that initiators interact with DNA in order to induce a more or less irreversible mutation. Promoters permit selection of mutant cells by inducing cell replication.

RADIATION ENERGY

Radiation, whatever its source (sunlight, X-rays, nuclear fusion or radionuclides) is an established carcinogen:

- X-Rays workers develop skin cancer and leukaemia.
- Therapeutic administration of radioisotopes
- Industrial processes involving radioactive substances

Hiroshima and Nagasaki atomic blast survivors disclosed a markedly increased incidence of leukaemia subsequent to an average latent period.

Treatment of arthrits using therapeutic irradiation may result in increasing incidence of leukaemia or bone cancer (osteosarcoma) years later.

Low and progressive doses of radiation should be administered to develop cancer. High doses will provoke a fatal mutation and lead the cell to die (apoptosis or necrosis)

Mechanisms of radiation carcinogenity remain unclear.

- X-Rays produce changes in DNA resulting in mutant cells.
- X-Rays induce the transformation (activation) of protooncogenes into oncogenes.
- X-Rays may induce a rupture of the chromosome resulting in translocations

BIOLOGICAL AGENTS

a. **Oncogenic viruses**. I. Nitulescu divided viruses into three categories according to their cellular effect:

- **Lytic viruses** that destroy cells, e. g. *Influenza* viruses.
- **Lysogenic viruses**: viral DNA becomes integrated within host genome. Years later it would become lytic and destroy host cells.

• **Oncogenic viruses** (both RNA and DNA containing viruses).

RNA viruses affect DNA synthesis through a particular mechanism. The RNA virus enters the cellular cytoplasm where it produces the RNA-dependent enzyme **DNA polymerase**. DNA polymerase copies RNA to make DNA. The virus is thereby able to insert complementary DNA into host DNA. This enzyme was isolated in a series of human leukaemias. According to their oncogenic effects upon normal cells, oncogenic RNA viruses may be classified into two categories:

• **Acutely transforming viruses,** possessing viral oncogenes, that is able to transform cells in culture fairly rapid.

• **Slow transforming viruses**: retroviruses that lack an oncogen may cause cancer by the following mechanisms:

- inducing a mutation of the protooncogenes and activates the protocogene and transform it to an oncogene
- viral RNA binds host DNA in the vicinity of a protooncogene and transform it to an oncogene(insertional mutation)

DNA viruses are directly incorporated into cellular genome. The *Epstein-Barr's* virus is a DNA virus directly associated with human neoplasia. Infection with Epstein-Barr's virus causes:

• **Mononucleosis** bening infection, when host immune system is normal so that virus may be cleared.

• **Burkitt's lymphoma**, or **naso-pharyngeal cancer**, if patient's immune system is made incompetent by a concurrent malaria infection; the situation is common in Africa.

GENETIC FACTORS

The hypothesis that the origins of cancers lie within cellular genes grows ever stronger. The proposed model is the following.

Cellular growth should be controlled by two different categories of genes:

• **Protooncogenes** stimulate cellular growth and proliferation.

• **Antioncogenes** are recessive oncogenes able to inhibit cellular proliferation.

The first: **protooncogenes** are highly conserved in nature because of their vital functions in normal cells. Sequences in cellular protooncogenes are closely homologous to viral oncogenes. Homology points to capturing of cellular genes during evolution by acutely transforming viruses. The functions of protooncogenes are the following:

• Encoding of proteins stimulating cellular development, the growth factors.

• Encoding receptors for growth factors

• "Ras" oncogene encodes G-protein- like molecules that transmit the growth message from cellular membrane to nucleus. Subsequent to their intrinsic GTP-ase activity, normal G-proteins bind GTP in the active form and GDP in the inactive form. Hence, this growth stimulus is not permanent, it occurs only in a specific moment of the cell development Abnormal G- proteins lacks GTP- ase activity and maintains a continous proliferation of cells.

Protooncogenes may become oncogenes (cancer provoking genes) if the following three conditions are achieved:

• **Point mutations:** replacement of a nuclear base with other

• **Translocation,** i. e. during chronic myelocytic leukaemia crossing-over between **abl** protooncogenes of the 9-th chromosome and **bcr** protooncogene from the 22-th chromosome occurs, resulting in a combination (hybrid of genes) with oncogenic activity.

• **Virus activation** : insertionnal mutagenesis

Thus, modified genes are called oncogenes. The oncogen proteins are named **oncoproteins** and they are abnormal variants of protooncogenes types:

• Abnormal growth factor, possessing an autocrin action(the action of the growth factor is exerted on the same cells that release it)

• Abnormal receptor: it is permanently activated in the presence of low concentrations of growth factor, inducing a permanent cellular mitogenic stimulus.

• Abnormal *ras* oncogene protein is a "G-protein" possessing only little GTP-ase activity, so that mitosis is permanently activated.

Recessive oncogenes (antioncogenes) exert the following functions:

• Encode membrane proteins that are responsible for contact inhibition of the cells - cellular mitosis is thereby stopped related to environmental occupation by other cells(hepatocytes do not excessive growth to occupy all the abdomen)

• Encode proteins responsible for stopping the cellular cycle at the G0 phase :

- The gene encoding protein p53 is activated to be expressed if a DNA mutation appears. The protein will stop the cellular cycle in G1 phase, during which the repair enzymes will cut the abnormal DNA and resynthetise other (repair the mutation). P53 is thus considered the policeman of the cell.
- Protein Rb cooperates with p53 in its action.

These genes are also called recessive genes because they act in a recessive way: both aleles must be modified to become able to develop cancer.

Mechanisms of Rb gene function: patients suffering from familial retinoblastoma display a mutant Rb allele and therefore only a single normal Rb gene may be found within all the cells of the body. The second mutant occurs during the life of this Rb gene, inducing definitive loss of Rb gene and subsequent onset of retinoblastoma. Biallelic mutations of p53 lead to the abnormal continuation of the cellular cycle and persistance of the error.

Ultra - violet rays causes modifications of the nucleic pairs of bases. Enzymes repair these errors. If patients feature a hereditary loss of these enzymes they may develop malignant melanoma. The disease is called **xeroderma pigmentosum.**

IMMUNOLOGICAL FACTORS

Clinical evidence of immunological response to tumours. Cancers featuring inflammatory infiltrates around the tumoral masses permitt a better prognosis. In early stages of neoplasms increased levels of both gamma-globulins and of the phagocytic index of the leukocytes may be found. Cancers occur more frequently in patients with deficiences of the immune system.

Several types of antigens exist in both viral and carcinogen-induced tumours:

- tumour-specific transplantation antigens (TSTA) that are specific to each tumoral tissue. These antigens are able to stimulate the response of both B-lymphocytes (antibodies synthesis) and T-lymphocytes (cellular immunity). Since T-cells only resognise the MHC antigens, these antigens are expressed on cell membrane together with MHC antigens.
- tumour-associated antigens. They are also present in normal tissues, since the **onco-fetal antigens** are found in fetal tissues. Fetal liver but not adult liver secretes **alpha feto-protein**. Since liver cancer secretes alpha feto-protein, the protein is considered to be a tumoral marker for this type of cancer. **Carcino-embryonic antigen (CEA)** is secreted by both fetal gastro-intestinal tract and colon carcinoma.

Unlike TSTA, onco-fetal antigens are not immunogenic; they are useful to predict the course of the disease (their serum level may be considered a marker of the disease)

Nature of tumour immunity. Specific types of cells mediating the tumoral immunity include:

- Cytotoxic T-cells able to recognise membrane TSTA-associated MHC-antigens.
- Natural killer cells able to destroy tumour cells without specific sensitization.
- Macrophages that are activated by T-cell derived gamma-interpheron and are able to kill tumour cells by 2 mechanisms:
  1. TNF generation

2. Oxygen free radicals generation (similarly to bacterial phagocytosis).

Humans possess a self-policing immune system. Unfortunately, most cancers would escape and develop. What should be the mechanisms underlying these mistakes?

1. Humoral blocking factor: antibodies block tumoral antigen sites so that T-cells are unable to recognise tumoral cells.

2. A tumour lacking antigen exposure or possessing low amounts of tumour antigens is unable to provoke an immune response.(in fact cancerous cells with a less density of antigenes are selected to growth)

3. Cancer cells express low levels of MHC antigens so that T-cells do not recognise the tumour antigens.

4. Immunosupression:

- Carcinogen factors usually induce immunosupression
- Tumour cells release a series of factors that depress the immune response - such as beta transforming growth factor (TGF - beta)
- Anticancerous treatment (cytotoxic drugs) is immunosupressive.

3. General effects of tumours upon hosts:

a. **Cancer cashexia** (progressive loss of body weight)

The origin of cancer cashexia remains unclear:

- Depression of the appetite resulting from tumoral secretion of TNF and IL1 that both inhibit the hypothalamic center of appetite resulting in reduced food intake. These cytokines are called cashectines.
- Infection of the tumor and fever induced hypermetabolism
- Tumour growth calls for more substances than the whole organism (cancerous tissue has the most intansive metabolism of all tissue of the body).

b. **Anaemia**

- Bleeding of the digestive cancers
- Metastasis within bone marrow
- Haemolyitic anaemias during lymphoid malignancies

c. **Fever:**

- Ulceration with the subsequent infection
- Pyrogenes in the malignant leukocytes
- Peritumoral inflammation

d. **Leukocytosis**, often accompanied by predominence of **eosinophils** or **monocytes**

e. **Sedimentation rate** and **fibrinogen** levels are increased

f. **Erytrocytosis:** erytropoetin in the case of a renal cancer or some other tumours (liver, cerebel)

g. **Coagulation and fibrinolytic status abnormalities:**

- Elevated platelet count
- Hypercoagulable state developing recurrent thromboembolic phenomena
- Disseminated intravascular coagulation (DIC) in mucus producing adenocarcinomas. DIC is triggered by mucus induced activation of factor X resulting in microangiopathic haemolytic anaemia: deposition of microvascular fibrin makes red cells unable to travers vessel lumen without suffering membrane damage.

4. **Paraneoplastic syndromes** (PS).

PS are clinical endocrine and neurological symptoms associated with tumours; at the same time, the cancer does not directly affect endocrine glands or nervous system.

a. **Hypercorticism (Cushing's syndrome).** It results from ectopic production of adrenocorticotropic hormone-like (ACTH-like) or corticotropin-releasing hormone (CRF-like), leading to increased adrenal production of glucorticoids, mineralocorticoids and androgens. Trunkal obesity, hirtsutism, hypertension and hyperglicemia should all appear subsequently. Lung carcinoma is particularly associated with this syndrome.

b. **Hypercalcemia**:

- **Hyperparathyroidism**: some tumours produce PTH-like substances (they are functionally similar to PTH). PTH provokes

- calcium renal reabsorbtion
- calcium release from bone to blood

Hypercalcemia may be a fatal PS syndrom.

- **Prostaglandin secretion**: breast carcinoma secretes Pg E2 that provokes serum calcium elevation by increasing osteoclastic bone resorbtion.
- **Bone metastasis** are facilitated by an increased Pg E2 synthesis.

c. **Inappropiate secretion of antidiuretic hormone (ADH-like).** Shwartz-Bartter's syndrome is most commonly found in lung small-cells carcinoma. ADH, by causing water renal reabsorbtion, results in hemodilution- induced -hyponatremia that may lead to depressed mentation, seizures, cerebral edema and death.

d. **Hypoglicemia**:

- Beta-cells pancreatic tumours may result in excessive insulin secretion.
- Some liver cancers secrete somatomedins (insulin-like groth factor, EGF)

e. **Other hormone-related syndromes.** Rare tumours have been shown to produce a variety of hormones or hormone-like compunds, including thyroid stimulating hormone, gastrin, secretin and glucagon.

f. **Neuro-muscular syndromes:**

- **Myasthenic syndromes** are mediated through poorly understood immunologic mechanisms, most probably antibodies against muscarinic receptors of the neuromuscular end plat. Myasthenic patients develop progressive weakness particularly in the respiratory muscles.
- **Degenerative neurologic syndromes**: peripheral neuropathies with both motor and sensory dysfunction occurs. Its mechanisms remain obscure but in some patients antibodies reacting with the neural tissue have been identified.

5. Metastasis

The development of secondary implants, discontinuous with the primary tumour, usually in remote tissues, is called **metastasis.**

Malignant tumours disseminate following several pathways:

- Seeding within body cavities
- Lymphatic spread
- Hematogenous spread.

1. **Seeding within body cavities:**

- Colon carcinoma can penetrate the wall of the gut and distantly reimplant in the peritoneal cavity
- Ovarian cancers characteristically cover peritoneal cavities
- Lung cancers pursue a similar sequence within pleural cavities.

2. **Lymphatic spread** is commonly met in carcinomas.

Lymph node enlargement implies:

- cancerous infiltration: lymphatic metastasis
- reactive changes (e. g. hyperplasia) are evoked into the node by the necrotic products of the neoplasm and the tumoral antigens.

The pattern of lymph node involvement should be different depending on the site of the primary tumour; thus, breast carcinoma first spreads to the axillary nodes.

3. **Hematogenous spread** is typical of sarcomas.

The first step is the invasion of veins by the primary tumour; subsequently, tumoral cells may disseminate as:

- hematogenous cells
- tumour emboli
- certain types of cancer are particularly able of growing within veins in a continuing manner.

The ability to metastasis is dependent upon **invasiveness**, which is a complex phenomenon involving the following:

- Cancer cells attachment to laminine in the basal membrane. Since cancer cells possess laminine receptors around their cellular membrane they should be able to attach to the basal membrane.
- Cancer cells migration within the connective tissue is related to their ability to release proteases and subsequently to digest the tissue.

6. Cancer biology.

Cancer develops succeeding to a latent period that follows the action of a chemical carcinogen. The tumour is initially monoclonal since it is the result of a single mutant cell. Increased proliferation should subsequently provoke some other mutation (mutant error) so that the cancer turns to be polyclonal in latter phases.

Homeostatic mechanisms to prevent cellular over-growth are acting in normal individuals so that cell birth is equal to cell death.

Conversely, cancer cells lack growth-restraining factors such as adjacent cell contact and therefore grow in an exponential manner.

Tumours are able to secrete angiogenetic factors and so form tumoral vasculature. Nevertheless, an imbalance between tumour size and tumour perfusion occurs in late stages, leading to tumour necrosis.

Inside a malignant tumour, only some cells are in an active state so that cancer cells may be divided into the following:

- Dividing cancer cells: they are sensitive to drugs;
- Temporarly non-dividing cancer cells that are partially or completely insensitive to drugs;
- Cancer cells that have irrevocable lost their proliferative ability.

In late stages, the non-dividing compartment enhances and and cancer should be treated using surgery and anti-tumoral drugs.

Stages of the carcinogenesis: the proces takes place step by step, a number of 4-12 mutations are necessary for tumor appearance.

1. **Initiation**: the carcinogene induce a protooncogene modification, which may become under the influence of the repair enzymes. Teir innability results in the following stage
2. **Promotion**: the substances called promoters will select the canceorus cells to stimulate them for growth; the cell become thus a precancerous cell
3. **Conversion**: the transformation of the precancerous cell to a cancerous one need one mutation to a sensible site of DNA called oncogene or antioncogene
4. **Progression:** it is the process by which the cancer becomes more malignant, by the following modifications:

- increased rate of proliferation
- other mutations, which enhance metastatic abilities
- polyclonality: the cells become different by the way their sensitivity to cytotoxic drugs, apoptosis, immunogenic properties

Tumoral markers:

1. Carcinoembrionic antigen: for cancer of the colon, pancreas, stomach, breast
2. Alpha-fetoprotein: for cancer of the liver or testis
3. Chorionic gonadotropin: ovary, lung, pancreas
4. Prostate specific antigen: prostate

I.12. PATHOPHYSIOLOGY OF HEAT REGULATION

HEAT REGULATION DISTURBANCIES

Average body temperature normally ranges between 36,7° C and 37° C. Temperature differs in various parts of organism, core temperatures being higher than those at the skin surface. Rectal temperature is commonly used to measure core temperature and is approximately 0,6° C higher than skin temperature.

1. BODY TEMPERATURE REGULATION

Body temperature is controlled by balancing heat production against heat loss. Since virtually all heat loss occurs through surface phenomena between the body and the environment, it is simply to understand the importance of the integument in the conservation or dissipation of the heat from the body core. Regulatory mechanism mainly involves changes of the blood flow through skin: blood flow enhancement results in heat dissipation while decrease preserves body heat.

Heat is transported to the surface and subsequently lost when skin and subcutaneous tissues circulation is enhanced; moreover, sweating enhances heat loss in a sometimes tremendous manner by providing water to be vaporized, so that up to 1 liter per hour of sweat may be evaporated. Environmental humidity decreases the ability of loosing heat by sweating.

Heat conservation is related to skin and subcutaneous tissues vasoconstriction.

Skin blood flow is regulated by neural mechanisms in which afferent nerves detects either worm or cold conduct impulses to the hypothalamus while efferences from hypothalamus cause direct either vasoconstriction or vasodilatation by sympathetic nerves. Sweating should be a major mechanism for temperature homeostasis.

1.1. Mechanism of heat production. Heat production is one of the principal by products of metabolism and its rate, also called *metabolic rate of the body*, is related to:

- Muscular activity including shivering muscular contractions
- Basal metabolic rate in all body cells
- Increases in metabolism resulting from the effect of thyroxin upon cells
- Cellular effect of epinephrine and norepinephrine sympatetic stimulation
- Heat generation in the body from deep organs such as liver, brain, heart and skeletal musculature
- Extra metabolism caused by increased temperature of the body cells themselves

1.2 Mechanism of heat loss. When heat is transferred from deeper organs to skin it may be lost through the following physical mechanisms: radiation, conduction, convection and evaporation.

Conduction consists of a direct transfer of heat from one molecule to another, including direct convection from skin to contact objects, e. g. a chair or a bed. Conduction of heat from the body to the air is self- limited unless the heated air is ntinually brought in contact with the skin.

Radiation is an exchange of electromagnetic energy between the body and the environment, in the form of infrared heat rays. Heat is transferred through air and subsequently environmental temperature should be lower than body temperature to give rise to heat loss by radiation. Therefore, if the temperature of the body is grater than the temperature of the surroundings, a greater quantity of heat is radiated from the body than is radiated to the body.

Convection is the transfer of heat to a fluid medium responsible for both the transfer of heat from cells to bloodstream and heat transfer through the circulation of air currents. When the body is exposed to wind, the layer of air immediately adjacent to the skin is replaced by new air much more rapidly than normally and heat loss by convection increases accordingly. The rate of heat loss to water at moderate temperature is many times as great as the rate of heat loss to air of the same temperature.

Evaporation converts liquid water that diffused to skin surface by sweating to vapours releasing body heat. Even when a person is not sweating, water still evaporates insensibly from the skin and lungs at a rate of about 600 milliliters per day. Unfortunately, this insensible evaporatin through the skin and lungs cannot be controled for purpose of temperature regulation because it results from continual diffusion of water molecules through the skin and respiratory surfaces regardless of body temperature. However, loss of heat by evaporation of sweat can be controlled

by regulating the rate of sweating. Evaporation is a necessary refrigeration mechanism at very high air temperature. When the temperature of the surroundings is grater than that of the skin, instead of losing heat, the body gains heat by radiation and conduction. Under these conditions, the only means by which the body can rid itself of heat is evaporation.

The skin, the subcutaneous tissues and the fat of the subcutaneous tissues are a heat insulator for the body. Blood vessels penetrate the fatty subcutaneous insulator tissues and are distributed profusely imediately beneath the skin. Especially important is a continous venous plexus that is supplied by the inflow of blood from the skin capillaries. In the most exposed areas of the body (the hands, ears, feet) blood is also supplied to the plexus directly from the small arteries through arteriovenous anastomoses. The rate of blood flow into the plexus can vary from barely above zero to as great as 30 percent of the total cardiac output by the degree of vasoconstriction of the arterioles and arteriovenous anastomoses that supply blood to the venous plexus of the skin. This is the most important mechanism of heat transfer from the body core to the skin.

1.3. Temperature control "set – point" concept.

The temperature of the body is regulated almost entirely by nervous feedback mechanisms and almost all of these operate through temperature regulating center located in the hypothalamus.

At a very critical body temperature, at a level of almost exactly 37°C, drastic changes occur in the rates of both heat loss and heat production. For example, at temperatures above this level, the rate of heat loss is grater that of heat production, so that the body temperature falls and reapproaces the normal level. The critical temperature level is called *set- point* of the temperature control mechanism. All the temperature control mechanisms continually attempt to bring the body temperature back to this set- point level.

The termoregulatory center belongs to the hypothalamus. Anterior hypothalamic preoptic area contains large amounts of neurons that functions as sensors for the central temperature but afferences also come to the hypothalamus from unmyelinated peripheral receptors from all over the body. A fall in a central temperature results is activating heat production and conservation mechanisms while a rise in central temperature activates heat loss mechanisms and therefore a negative feed – back control system occurs.

Prostaglandins of E series (PgE) play a major role in mediating events concerning temperature regulation within the hypothalamus. They cause α - andrenergic receptors to release cyclic adenosine monophosphate (AMP), which in turns alters the Ca2+/ Na+ ratio. This alteration results in firing of efferent neurons in the anterior hypothalamus.

However, for these feed- back mechanisms to operate, there must also exist temperature detectors called temperature receptors in the skin and deep organs (spinal cord, abdominal viscera and around the great veins).

1.4. Temperature decreasing mechanisms when the body is too hot:

1.4.1 Superficial blood vessels dilation. Blood containing core heat is delivery to the periphery where heat is dissipated through radiation, conduction and convection. Mechanisms of this effects involve inhibition of sympathetic vasoconstrictors centers from the posterior hypothalamus.

1.4.2 Sweating. Sweat evaporation results in heat loss. An aditional 1°C increase in body temperature causes enough sweating to remove ten times the basal rate of body heat production.

1.4.3 Hyperpnea

1.4.5 Decrease of heat production. Those mechanisms that cause excess production, such shivering and chemical thermogenesis, are strongly inhibited.

1.5 Temperature increasing mechanisms when the body is too cold:

1.5.1 Superficial blood vessels vasoconstriction. Both reduction of blood flow through skin and subcutaneous tissues and circulation confinement to inner body structures prevent loss of core heat. Posterior hypothalamic sympathetic center is responsible for this effect.

1.5.2 Piloerection (contraction of the pilomotor muscles surrounding hair in the skin) results in a thick layer of insulator air next to the skin so that the transfer of heat to the surroundings is greatly depressed. Sympathetic stimulation causes the arrector pili muscles attached to the hair follicles to contract.

1.5.3 Shivering increases heat production by extremely rapid clonic muscular contractions directed by the hypothalamus shivering motor center. This area is normally inhibited by signals from the heat center in the anterior hypothalamic area but is excited by cold signals from the skin and spinal cord. This center becomes activated when the body temperature falls even a fraction below the critical temperature level. It then transmits signals through bilateral tracts down into the lateral columns of the spinal cord and finally to the anterior motor neurons. These signals are nonrhythmic, they increase the tone of the skeletal muscles. When the tone rises above a certain critical level, shivering begins. This probably results from feedback oscilation of the muscle spindle stretch reflex mechanism.

1.5.4 Increased production of epinephrine and thyroid hormone enhances cellular metabolism rate resulting in the **chemical thermogenesis.** It results from the ability of these hormons to uncouple oxidative phosphorylation, so that energy is lost in the form of heat not in the form of ATP. The degree of chemical thermogenesis is directly proportional to the amount of brown adipous tissue, that contains large

number of mitochondria where uncoupled oxidation occurs. These cells are supplied by a strong sympathetic innervation.

2. INCREASED BODY TEMPERATURE

Fever and hyperthermia refer to an increase in body temperature above the normal range.

2.1 Fever.

2.1.2 Definition: A disorder of thermoregulation involving an upwards displacement of the hypothalamic set – point for temperature controll regardless of the ambient temperature. It is a special hyperthermal situation. Hypertermia from other causes is not accompanied by a resetting of the central thermostat.

2.1.2 Etiopathogenesis. Fever is caused by a series of substances that collectively incite the production of the fever producing, mediators called "pyrogens". Pyrogen – producing substances include viruses, bacteria and other microorganisms, inflammatory products, antigen – antibody complexes, drugs and chemicals.

Fever may occur in various conditions, including: infections, immunologic disorders, infarction, tissue trauma, granulomatous disorders, inflammatory bowel disorders, neoplastic disorders, acute metabolic and endocrine diseases such as gout, thyroid crises and pheochromocytoma.

Non – infectious diseases featuring fever include: myocardial infarction or cancers through abnormal proteins releases; leukaemia and Hodgkins' s disease (their malignant cells secrete endogenous pyrogens); cerebral trauma, intracerebral bleeding or increased intracranial pressure provoke neurogenic fever.

When the cause of fever cannot be found, the condition is termed fever of undetermined origin (FUO). It occurs particularly during the following pathologic states: infection (40%), cancer (30%), immunogenic disorders (20%) and in 5 to 9% no predisposing condition may be found (table 8).

Pyrogen – producing substances are ingested by macrophages which are thereby activated and subsequently release an endogenous pyrogen identified as **interleukin – 1 (IL 1).** IL 1 produces fever by increasing the set – point of the hypothalamic thermoregulatory center. Seemingly, IL 1causes fever by stimulating the synthesis of PgE and particularly PgE2. PgE formation blocking by drugs such as Aspirin results in either partial or complete decline of fever. Conversely, since IL 1 levels are not increased in normal subjects, body temperature in normal individuals should not be lowered by Aspirin.

Table 8: Diseases accompanied by fever

Disease state	Mechanism
1. Infections	Septic inflammation
2. Diseases due to immune mechanism (connectiv tissue diseases, immune induced hemolysis, drug reactions, AIDS)	Allergic inflammation Infectious complications due to immunosupression
3. Tissular damages (crushing mechanical trauma, ischemic infarctions, thrombosis, rhabdomyolysis)	Resorbtion of the damaged proteins
4. Granulomatous diseases (tuberculosis, sarcoidosis)	Granulomatous chronic inflammation
5. Intraabdominal inflammatory processes (hepatitis, pancreatitis, chronic bowel inflammations)	Septic or necrotic inflammations
6. Neoplastic disorders	Peritumoral inflammation (considered a nonspecific defence mechanism) Metastasis Release of pirogens from the malignancies of the lymphoreticular and hematopoetic system
7. Acute metabolic disorders: • gout, porphyria • thyroid crisis, pheochromocytoma • Addisonian crisis	Inflammation Increased of thermogenesis Decreased thermolysis (dehydration)

Endogenous pyrogen (EP) is formed by a variety of body cells, but especially the granulocytes leukocytes. It is released from leukocytes following ingestion of endotoxin, viruses, bacteria or other foreign materials. EP does not seem to be stored performed in leukocytes, but is rapidly manufactured by them. Other cells capable of producing EP include eosinophils, monocytes, Kupffer' s cells, tissues macrophages and certain tumour cells. Lymphocytes do not produce EP but activated lymphocytes release lymphokines that stimulate EP production by granulocytes. EP exerts its actions mainly upon anterior hypothalamus; it plays a major role in elevating body temperature.

Besides IL 1, a series of substances have been identified as EP, including tumour necrosis factor – alpha (TNF- α), interleukin – 6 (IL 6) and alpha -, beta and gamma – interpherons.

The main actions of IL 1 and TNF – alpha which are characteristic of the acute inflammatory response are mentioned in the table 9. Many of these actions also involve arachidonate intermediates.

Table 9: Systemic effects of IL-1 and TNF

ACTION	SYSTEMIC SYMPTOMS
1. Induce PgE syntesis in the anterior hypothalamic centers.	Fever
2. T – cell: initiate immune response by activating helper/ inducer T – cells to secrete IL 1 B – cell: proliferation and specific antibodies production	Fever
3. Mobilizes myeloid cells from bone marrow storage pools	Leucocytosis
4. Stimulates microbicidal oxidative metabolisms of the mature neutrophils	Leucocytosis
5. Induction of cell – adhesion molecules	Inflammation
6. Platelet activating factor production	Inflammation
7. Fibroblasts proliferation and collagen synthesis	Tissue reparative response during infection
8. Increased skeletal muscle proteolysis	Weight loss
9. Inhibition of appetite	Weight loss
10. Liver proteolysis and glycogenolysis	Hypercatabolism
11. Liver synthesis of acute phase proteins	Inflammation
12. Vasodilation	Hypotension; malaise
13. Endocrine response: releasing of ACTH, beta – endorphines, cortisole and cathecolamines	Endocrine support for febrile reaction
14. Activation of cerebral neurons responsible for slow – wave sleep signals through IL 1 contained and released by astrocytes	Drowsiness

By this means fever, as part of the innate inflammatory response, may exert a positive feedback on the specific immune response.

Exogenous pyrogens are derived from outside the host; most are microbes, microbial products or toxins. They cause fever by inducing release of EP, which are polypeptides produced by various host cells (especially monocytes – macrophages).

Accompaniments of fever: systemic symptoms:

- Chills: because the blood temperature is less than the setpoint of the hypothalamic temperature controller, the usual responses that cause elevation of body temperature occur. During this period the person experiences chills and feels extremely cold. Also the skin is cold because of vasoconstriction and the person shivers.
- Changes in mental status: irritability, drawsiness or delirium are more strking in the very old or very young. The soporific actions of TNF and IL- 1 as well as release of β- endorphins may contribute to these events.

- Convulsions: infants and childreen less than age 5 may develop seizures when the temperature is elevated.
- Sweats: when the stimulus of the fever production is removed by the action of antipyretics, defervescence is achieved by activation of diffuse sweating.
- Herpes labialis: elevation of body temperature can activate latent herpes simplex virus infection.

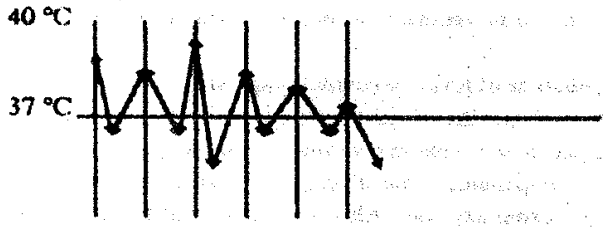
2.1.3 **Course** may be divided into four stages:

- **Prodrome** resulting from phyrogen production subsequent to macrophage activation by the etiologic factors.
- **Chill** occurs when the hypothalamic set – point is suddenly switched from normal a to higher value and body temperature subsequently trends to reach the new temperature. Elevation of body temperature is related to:
  - Cutaneous vasoconstriction (the skin is cold).
  - Shivers
  - Piloerection
  - Ephinephrine secretion
- **Flush** appears when body temperature has reached the new hypothalamic set – point; the shivering ceases and the patient perceive a sensation of warm. Skin becomes warm and flushed because of the cutaneous vasodilation.
- **Defervescence** . The set – point of the hypothalamic center is suddenly reduced to a lower value. Activation of the anterior hypothalamic area provokes sweating and vasodilation and thus body temperature turns to normal.

2.1.4 Patterns

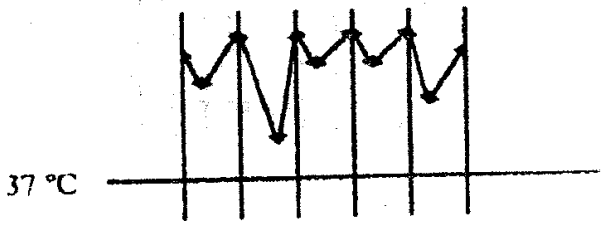
Fever patterns may provide information about the provoking condition.

In intermittent fever temperature falls to normal at least once 24 hours. When the variation between the pick and the nadir is very large the fever is called hectic or septic.

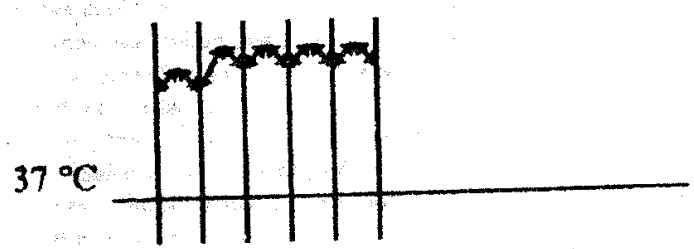


Intermittent fever is commonly met in pyogenic infections (particularly abscesses), lymphomas and milliary tuberculosis.

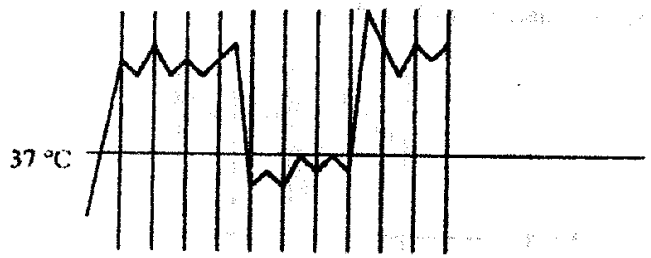
In **remittent** fever. temperature varies a few degrees in either direction every day but does not return to normal. Most fevers are remittent and this type of febrile response is not characteristic of any disease.



Sustained (continous) fever is characterized by persistent elevation with minimal diurnal variation. Untreated typhos commonly features this kind of fever.



In **relapsing** fever short febrile periods occur between one or several days of normal temperature. E. g. malaria, urinary tract infection, Hodgkin' s disease feature relapsing fever.



2.1.5 Purpose

There is a great deal of discussion about whether fever is beneficial or harmfull to humans.

Benefit of fever

Fever is a valuable index to health status. It has been shown that small elevations in temperature accelerate both catabolic processes involving mobilization of aminoacids from muscle and specific immune responses. These events are mediated by IL 1 and involve synthesis of PgE. Increased motility and activity of leukocytes, enhanced phagocytosis and chemotaxis by human polymorphs, as well as raised interpheron production and T – cells activation have also been noted. Body temperature within fever range inhibit bacterial growth. There are a few infections in humans in which pyrexia appears definitely to be beneficial to host, such as neurosyphilis, some forms of chronic arthritis and widespread cancer. Certain other diseases such as rheumatoid arthritis sometimes improve after fever therapy. Conversely, aged and debilitated patients with infection may have little or no fever and this is generally interpreted as a bad prognostic sign.

Detrimental aspects of fever.

Fever accelerates many metabolic processes and is accompanied by IL 1 mediated muscle wasting and weight loss. Sweating aggravates loss of salt and water. There may be discomfort due headache, fotofobia, general malaise or unpleasant sensation of warmth. Heart rate and heart work are related to temperature elevation and normally a 1° C rise in temperature produces a 15 beat/ minute increase in heart rate. Profound modifications of both cardiovascular and respiratory systems occur during fever and thus dangerous consequences may result in elderly patients suffering from chronic respiratory disorders, either overt or potential cardiac diseases or general vascular diseases. Fever may also precipitate seizures in epileptic patients.

Patients with fever should be generally treated with antipyretics. But, since fever may be of some benefit milder levels of fever should be less intensely lowered. Mild analgesics which are often also antipyretics should relieve the discomfort that often accompanies fever.

2.2 Hyperthermia

Hyperthermia describes an increase in body temperature that occurs without a change in set-point of the hypothalamic thermoregulatory center. A number of favouring factors including prolonged muscular exercise performed in warm environment e. g. by athletes may result in hyperthermia.

2.1.1. Heat stoke

Heat hyperpyrexia, heat stroke or sunstroke in a severe failure of the thermoregulatory mechanisms resulting in an excessive rise in body temperature, greater than 40 °C.

It is most common in elderly individuals with preexisting chronic disease, including arteriosclerosis, congestive heart failure (particularly when patients receive diuretics), diabetes mellitus, alcoholism and skin disorders that interfere heat loss, such as scleroderma. Predisposed individuals may also feature a decrease perception of environmental temperature and a failure in homeostatic mechanisms.

Symptoms are related to the onset of a hypovolemic shock resulting from an excessive loss of fluids and electrolytes in sweat. There is a limit to the rate of which the body can lose heat even with maximal sweating. Furthermore, when the hypothalamus becomes excessively heated, its heat- regulating ability becomes greatly depressed and sweating diminished. As a result, a high body temperature tends to perpetuate itself . Hyperpyrexia itself damages body tissues and particularly the brain, the liver and the heart. The tissular damages are hemorrhages and parenchymatous degeneration of cells especially in the brain.

There may be few premonitory symptoms of heat stroke and loss of cosciousness may be the first sign. Headache, dizzines, vertigo, faintness, as well as hyperpnea may also appear in these patients. Damages to the liver, kidney or brain can often be great enough that failure of one or more of these eventually causes death, sometimes not until several days after the heat stroke.

2.1.2 Malignant hyperthermia (MH) cosists of a group of inherited disorders that are characterized by a rapid increase in temperature to 39 °C – 40 °C in response to general anesthetics (halothane, cyclopropane, ethyl eter) and muscle relaxants. Body temperature may rise as high as 43 °C in certain patients and a first sign is the skeletal-muscular rigidity. In one form of the disease where the mechanism of

inheritance is autosomal dominant, subjects are normal between attacks. A second recessive form occurs in young boys and, less commonly, girls, with a number of congenital abnormalities (short stature, lumbar lordosis, thoracyc kyphosis, pectus carinatum, small chin, low set ears). MH has also been described in several other myopathies including myotonia congenita, central core disease and Duchenne's muscular dystrophy.

Pathogenesis of MH. The triggering anesthetic releases Ca from the membrane of the muscle cell's sarcoplasmic reticulum, which is defective in storing this ion. Myoplasmatic Ca suddenly rises. Calcium activates myosin ATP-ase, wich converts ATP to ADP and heat. There are also inhibition of troponine, uncoupling of oxidative phosphorylation, activation of phosphorylase-kinase and incresead glycolysis. Muscular contraction occurs and it, as well as chemical events, leads to production of heat.

3. DECREASED BODY TEMPERATURE

Hypotermia is defined as a core temperature less than 35°C.

3.1 Physiologic hypotermia occurs in elderly and in children in which body temperature regulatory mechanisms are either depressed or imature.

3.2 Accidental hypotermia. This is a well known complication of exposure and has been reported frequently during winter. It usually occurs in elderly or inebriated patients after prolonged exposure to excessively low external temperatures. Subjects appear cold and pale and seem to display rigor mortis when their temperature is very low. If temperature is lower than 26°C patients are uncoscious and generalized oedema occurs. Laboratory findings should display the following:

- haemoconcentration
- mild azotemia
- metabolic acidosis
- haemoglobin dissociation curve is shift to the left
- hypoglycemia / hyperglycemia
- EKG bradicardia, slow atrial fibrillation.

3.3 Pathologic hypothermia is a decrease in core temperature resulting from the disorders of thermoregulatory mechanisms, including cardiovascular diseases e.g. cogestive heart failure, cerebrovascular diseases, malnutrition, hypothiroidism, diabetes and hypoglicemia, severe renal failure with uremia, acute respiratory failure, as well as the excessive use of sedative drugs. Exposure to small decreses in atmospheric temperature and alcohol intake are contributing factors, with regard to the inhibition of the thermoregulatory center. The entity differs from accidental hypothermia only in the absence of exposure. The mechanism appears to be an acute failure of thermoregulation; shivering did not accur in any of these patients.

With mild hypothermia, sympathetic nervous system system activity is raised, resulting in vasoconstriction, accelerated heart rate, increased stroke volume, slightly increased blood pressure and hyperventilation, as well as cold diuresis.

As hypthermia progresses, there is a gradual decline in heart rate and cardiac output. Ventricular fibrillation appear to be a major cause of death in hypothermia. Metabolic rate falls to 50% of normal at 28°C.

3.4 Frosbite refears to freezing of the surface area exposed to extremely low temperature. This occurs especially in the lobes of the ears and in the digits of the hands and feet. If the freeze has been sufficient to cause extensive formation of ice crystals in the cells, permanent damage may result, such as circulatory impairement, ischemia and tissue damages. Often gangrene follows and the frosbitten area is lost.

3.5 Controlled (artificial) hypothermia may be used during certain types of heart surgery to slow down and stop the heart and decrease brain metabolism. Thus, during induced hypothermia, both cellular oxygen demand and production of end products of metabolism (lactic acid) are decreased.. It is easy to decrease the temperature of a person by first administering a strong sedative to depress the reactivity of the hypothalamic temperature controller and then cooling the person with ice or otherwise until the temperature falls. Cooling to this extent does not causes severe pathophysiological results like accidental hypothermia.

II. SPECIAL PATHOPHYSIOLOGY

II.1. Pathophysiology of respiratory system

The essential function of respiration is to provide oxygen for and to remove excess carbon dioxide from the cells of the body. This involves the controlled absorbtion of oxygen to oxygenate mixed venous blood and the elimination of carbon dioxide so that normal blood gas tensions are maintained. Respiration in its clinical sense is generally restricted to these aspects which concern the major airways and lungs. Respiration in its broader physiological aspects context involves four processes. The first act of respiration is **ventilation** which is the exchange of gases between the alveolar spaces and external atmosphere. Then, in the lungs the blood gases exchange with alveolar air by **diffusion** across the alveolar walls. The blood is used to **transport** gases to and from the tissues, and **exchange** between blood and tissue cells occurs in the systemic capillaries.

Although primarily involved in gas exchange, the lungs also have important non-respiratory functions: they act as a filter for the blood passing through them and are also concerned in the metabolism of certain vasoactive substances. This is facilitated by the fact that all the blood passes through the lungs in a single circulation.

Significant proportion of circulating 5-hydroxitryptamine, bradykinin, prostaglandins and noradrenaline may be removed from the blood during its passage through the lungs. The lung is probably the main site for the conversion of the relatively inactive decapeptide angiotensin I to the potent systemic vasoconstrictive octapeptide angiotensin II. The enzyme mechanisms responsible for the clearing and activation of these vasoactive substances are probably localized in the endothelium of the pulmonary vessels.

CONTROL OF RESPIRATION

A number of mechanisms contribute to bringing air into the lungs so that exchange of gases can occur. The mechanical function of moving air in and out of the lungs is termed ventilation and is accomplished by a number of interacting components. Of particular importance is a reciprocating pump called **the repiratory bellows**. This bellows has two volume-elastic components: the lung itself and the chest wall surrounding the lung. The chest wall consists of the skeleton and tissues of

the thoracic cage, as well as the diaphragm, abdominal contents and abdominal wall. The respiratory muscles, which are a part of the thoracic wall, provide the driving force for the operation of the bellows. The diaphragm (assisted by those muscles that elevate the ribs and sternum) is the principal muscle involved in increasing the volume of the lung and thoracic cage during inspiration; expiration is a passive process during quite breathing.

The repiratory muscles are controlled by the respiratory center, which is composed of neurons and receptors located in the pons and medulla. The repiratory center is the part of the nervous system that controlls all aspects of breathing. The prime factor in the controll of breathing is the receptor of the central chemoreceptors in the respiratory center to the partial pressure of carbon dioxide (Pa CO_2) and the pH of the arterial blood. An increase in the Pa CO_2 or a decrease in the pH stimulates breathing.

A decrease of the partial pressure of oxygen in the arterial blood (Pa O_2) can also stimulate ventilation. Peripheral chemoreceptors located in the carotid bodies at the bifurcation of the common carotid arteries and in the aortic bodies at the aortic arch respond to decreases in Pa O_2 and pH and increases in Pa CO_2. The Pa O_2, however, must fall from the level of about 90 to 100 mm Hg to a level of about 60 mm Hg before ventilation is significantly stimulated.

Other mechanisms cotroll the amount of air taken into the lungs. As the lung is inflated, these receptors signal the respiratory center to stop further inflation. Signals from the stretch receptors cease at the end of expiration when the lung is deflated and the repiratory center is free to initiate another inspiration. These mechanism, known as **Hering - Breuer reflex**, is more important in new born babies than in adult unless tidal volume exceeds 1 liter as in exercise. Movements of joints and muscles (for example during exercise) also stimulate an increase in ventilation. Voluntary controll input from the cerebrum can modify output from the repiratory centers, thus allowing interruption of the normal breathing cycle for laughing, crying, and speaking.

II.1.1. PATHOPHYSIOLOGY OF RESPIRATORY FAILURE

The primary function of the lungs as stated is to add oxygen to and remove carbon dioxide from the circulating blood. Thus, **respiratory failure is defined in terms of hypoxemia, when the arterial oxygen tension has fallen bellow 60 mm Hg (8 Kpa) as a result of lung disease in a patient breathing air at sea level.** In some forms of respiratory failure there is associated carbon dioxide retention so that arterial tension of this gas rises above 45 mm Hg (60 Kpa). Respiratory failure is said to be of type I when there is no associated carbon dioxide retention and of type II when there is.

1. TYPE I OF RESPIRATORY FAILURE

Hypoxemia without carbon dioxide retention is common in many types of extensive lung disease: acute attacks of bronchial asthma; *pulmonary oedema*; pneumonia of whatever etioloy; pulmonary collapse; pulmonary thromboembolism and in extreme obesity, particularly when lying down. Interstitial lung disease such as fibrosing alveolitis, sarcoidosis, allergic alveolitis, asbestosis and other pneumoconioses are also recognized causes.

Arterial blood gas measurements define the status of gas exchange but are not diagnostic of any specific pathology in the lung. The low arterial carbon dioxide tension associated with the hypoxemia can cause respiratory alkalosis. A low carbon dioxide tension usually persists despite oxygen therapy; therefore, the alveolar hyperventilation causing this low carbon dioxide tension is not due to hypoxic stimulation of arterial chemoreceptors, but is most likely the result of the disease process stimulating intrapulmonary vagal afferent fibers, which then cause hyperventilation irrespective of the arterial oxygen tension.

Respiratory function tests may indicate the cause of the respiratory failure. Thus, a variable forced expiratory volume is one second (F.E.V. 1) in bronchial asthma contrasts with the persistently low F.E.V. 1 in chronic bronchitis and emphysema. Lung volumes are increased in this conditions. In contrast, in interstitial lung disease, all lung volumes are reduced. again, with low F.E.V. 1 and an impaired of difusion expresed by low capacity for diffusion of carbon monoxide across the alveolar - capillary wall. This is termed a restrictive pattern of respiratory function. In emphysema the low transfer factor for carbon monoxide is associated with a low F.E.V. 1 and an increase in both total lung capacity and residual volume.

Hypoxemia and hypoxia

The term *hypoxemia* refers to values of PaO_2 that are abnormally low and is frequentlly associated with hypoxemia or inadequate tissue oxygenation. Hypoxemia is not necessarily accompanied by tissue *hypoxia*. One can have normal tissue oxygenation with hypoxemia, just as one can have a normal PaO_2 with tissue hypoxia (because of the abnormalities of oxygen delivery and utilisation by the cells). There is a relationship, however, between the PaO_2 and tissue hypoxia, although the precise PaO_2 at which impairment of tissue use of oxygen occurs is variable. In general, PaO_2 values that are persistently less than 50 mm Hg are associated with tissue hypoxia and acidosis (caused by anaerobic metabolism). Because hypoxia may exist with both normal and low values of PaO_2, evaluation of blood gas measurements must always be correlated with clinical observation of the patient. Cyanosis is an unreliable sign of hypoxia because the oxygen saturation must be below 75% in persons with normal

hemoglobin before it is detectable. Clinical signs and laboratory findings that indicate hypoxia are listed in table 10 .

Tabel 10 - Indicators of hypoxemia and hypoxia

Arterial blood gases	Pa O_2: 80 - 100 mm Hg (normal) 60 - 80 mm Hg (mild hypoxemia) 40 - 60 mm Hg (moderate hypoxemia) < 40 mm Hg (severe hypoxemia) Sa O2: 95 - 97% (normal) <90% pH: 7,35 - 7,45 (normal) <7,35 (acidemia) Pa CO_2: 35 - 45 mm Hg (normal) > 45 mm Hg (hypoventilation) < 35 mm Hg (hyperventilation)
Respiratory system	Tachypnea; decresed tidal volumes; dyspnea; yawning; use of accessory respiratory muscles, flared nostrils.
Central nervous system	Headache (from cerebral vasodilation); mental confusion; bizarre behaviour; restlessness Agitation, anxious facial expression, sweating Drowsiness progressing to coma when hypoxia is severe
Cardiovascular system	Tachycardia early; bradycardia later, when heart muscle not receiving adequate oxygen Rise in blood pressure followed by a drop when hypoxia remains uncorrected; dysrhythmias
Skin	Cyanosis of lips, oral mucosa and nail beds.

Mechanisms of arterial hypoxemia

a. A low inspired partial pressure of oxygen in the ambient air occurs at high altitude; a lowered oxygen tension in inspired air may also occur if a patient is accidentally ventilated at low oxygen concentration, as from a faulty anaesthetic or inhalational therapy device. However, these are specifically excluded in the above definition of respiratory failure for there is no lung disease involved.

b. Mismatching of alveolar ventilation to perfusion is best illustrated by the extreme and theoretical situation where all the cardiac output goes to one lung and all the inspired air to the other, which is clearly incompatible with life.

Ventilation - perfusion inbalance is the commonest cause of respiratory failure in clinical practice and develops in most pathological processes which involve

substantial parts of the lungs such as chronic bronchitis and emphysema, bronchial asthma and pulmonary edema.

c. Alveolar hypoventilation causes hypoxemia associated with a high arterial carbon dioxide tension.

d. An increase in shunt fraction is blood passing from the right heart to the systemic arterial circulation without being oxygenated in the lung. The shunt fraction is increased in congenital right-to-left cardiac shunt, and is also the commonest cause of hypoxemia in pulmonary collapse. It also plays a role in the low arterial oxygen tension seen in both pneumonia and the adult respiratory distress syndrome.

e. The alveolar - capillary block syndrome describes hypoxemia brought about by interstitial lung disease due to thickening of the alveolar - capillry membrane.

In the normal lung, alveolar gas is separated from capillary blood by the alveolar-capillary membrane, which is composed of three distinct anatomical layers: alveolar epithelium, a narrow interstitial zone and capillary endothelium. It is now known that hypoxemia in this syndrome arises from a mismatch of alveolar ventilation to perfusion. It was thought that respiratory function tests designed to measure the diffusion of carbon monoxide across the alveolar - capillary membrane specifically identified this syndrome. This, however, is not true, because impaired diffusion of this gas also occurs where there is mismatching of alveolar ventilation to perfusion.

In clinical practice direct measurements of oxygen and carbon dioxide tension in arterial blood, with knowledge of the gas concentration being inspired at the same time, allows the difference between alveolar and arterial oxygen tension to be estimated with enough accuracy to separate these different mechanisms at the bed side.

f. The admixture of abnormal desaturated venous blood is an important mechanism acting to lower Pa O_2 in patients with lung disease and impaired pulmonary gas exchange. The mixed venous O_2 saturation is directly influenced by any inbalance between O_2 consumption and O_2 delivery. Thus, anemia uncompensated by an increase in cardiac output or a cardiac output insufficient for metabolic needs can cause Pa O_2 to fluctuate even the severity of lung pathology remains unchanged.

Common causes of type I respiratory failure:

Pneumonia
Bronchial asthma
Chronic bronchitis and emphysema (pink puffers)
Non-cardiogenic pulmonary edema
Pulmonary thromboembolism

Cardiogenic shock
Tension pneumotorax
Pulmonary fibrosis of any cause
Obesity

2. TYPE II OF RESPIRATORY FAILURE

This implies alveolar hypoventilation, most commonly from chronic bronchitis and emphysema. This may occur in an acute exacerbation with a raised carbon dioxide tension and low pH. When it is chronic and the arterial oxygen tension lowered to 50 mm Hg (6,65 kPa) and arterialo carbon dioxide raised to 50 mm Hg (6,65 kPa) the pH may be normal, acidosis being corrected by reabsorption of bicarbonate in the renal tubules. The severity of an acute exacerbation is thus shown by disturbance of the arterial pH more than the level of the arterial carbon dioxide tension in these patients. Alveolar hypoventilation can also arise if narcotic overdosage depresses respiration, in head injuries, with thoracic and chest wall deformities (e. g. kyphoscoliosis) or with trauma (e. g. crushed chest injury).

Three major mechanisms can cause or contribute to ventilatory failure:

a. Respiratory drive can be insufficient.

b. The work load can be too high either because too many litres of gas must be moved or because it is too costly in energy to move each litre of gas.

c. The ventilatory pumps may be defective because of structural problems in the chest wall, impaired muscle strength or in coordination.

a. Respiratory drive determinants

The sensitivity of the respiratory drive center to hypercapnea (and hypoxemia) is, in part, a congenital characteristic, but many potentially reversible factors also affect ventilatory drive. Drive intensity tends to fluctuate with metabolic activity. Thus, for the same level of Pa CO_2, the expired minute ventilation will vary with oxygen ventilation. Conditions such as hypothyroidism and malnutrition simultaneous depress the resting oxygen ventilation and the intensity of ventilatory drive. Other factors that contribute to reduced drive include sedatives, depressed mental status, chronic loading of ventilation (e. g. during a prolonged asthma attack), sleep deprivation and metabolic alkalosis.

b. Ventilatory work load requirements. The minute ventilation needed to maintain pH stability is influenced by CO_2 production, by the ventilatory dead space fraction and by the need to compensate for metabolic acidosis. CO_2 retention may be an adaptative change to reduce the work of breathing while eliminating CO_2 at the same rate at which it is produced. Apart from minute ventilation requirement, the

work per liter of ventilation is the other major component that determines the total work load.

Ventilatory work must be done primarily against functional and elastic forces.

Restrictive diseases of the lungs, pleural space or chest wall decrease the elastic component. Such problems are produced by any process that infiltrates lung, causes a reduction in the number of functioning units or impedes the lung from expanding.

Impeded lung can be result of problems, e. g. pneumothorax, pleural effusion or a chest wall made stiff by obesity, ascites or burn eschar. It is important to realise that a reduction in the number as well as in the caliber of airways influences the functional cost of ventilation. Air flow obstruction (e. g. bronchospasm, mucosal edema and accumulated secretions) increases the functional component and the energy cost of breathing rises strikingly as airways diameter decline.

c. **Pump function.** For effective ventilation pleural pressure must be developed by the respiratory muscles acting in coordinating fashion on an intact rib cage. Diseases (e. g. flail chest, kyphoscoliosis) may structurally alter the chest wall and cause **inefficient coupling** between muscles contractions and pleural pressure generation. Hypoventilation can also result when the inspiratory muscles of the diaphragm and rib cage contract asynchronously, as during diaphragmatic paralysis, quadriplegia or acute stroke.

In many instances, the primary reason for pump dysfunction is **reduced muscular power**. A key determinant of strength and endurance, total muscle bulk, relates to age, sex, body size and nutritional status. The performance of each muscle fibre is determined by precontractile muscle length, the velocity of shortening and the metabolic environement. Acid - base disturbances, acute CO_2 retention, O_2 deprivation, ischemia and deficiency of phosphate, Mg, K, Cl, K and iron impair fiber contractility. Even when the strength of individual muscle fibers is normal, acute **hyperinflation** seriously reduces the efficiency of the ventilatory pump. Not only are the inspiratory muscle fibers foreshortened so that they produce less force, but the elastic work that the muscle must do is also increased because of the residual end-expiratory recoil tension and reduced compliance of the lung's connective tissue elements at high lung volumes. Furthermore, altered geometry (e. g. the flattened diaphragmand expended rib cage) limits the pleural pressure change that can be developed during forceful contraction.

Common causes of type II respiratory failure

- Chronic bronchitis and enphysema (particularly in an acute excerbation)
- Kyphoscoliosis and other disorders of the thoracic cage
- Respiratory muscle failure (particularly in bilateral diaphragmatic palsy, when the patient lies supine.

- Muscular distrophy
- Poliomyelitis
- Peripheral neuropathy (Guillain - Barré's syndrome)
- Myasthenia gravis
- Head injury
- Narcotic overdosage
- Sleep apnea
- Postoperative
- Atelectasis

3. CLINICAL RECOGNITION

Because the clinical symptoms and signs of respiratory failure are non-specifc diagnostically and may be minimal in the presence of severe hypoxemia, hypercarbia and acidemia, the detection of respiratory failure of any cause depends on serial evaluation of arterial blood gases and pH.

Acute tissue O_2 desaturation affects cellular metabolism and, if severe, can cause irrversible damage to sensitive tissues (e. g. brain, heart) within minutes.

Acute hypoxemia may cause problems that range from cardiac arrythmia to coma. Although chronic depressions in Pa O_2 are generally well tolerated by patients with adequate cardiovascular reserve, alveolar hypoxia can induce pulmonary arteriolar vasoconstriction and increased pulmonary vascular resistance. Over days and weeks this process can lead to pulmonary hypertension, right ventricular hypertrophy (cor pulmonale) and eventual right ventricular failure.

Raised arterial and tissue p CO_2 affect metabolism primarily by altering acid - base balance. As with hypoxemia, the effects of acute hypercarbia are much less tolerated than chronic hypercarbia. Acute decreases in cerebral pH associated with increases in plasma and tissue p CO_2 increase ventilatory drive. However, over time, increased buffering capacity in the C.N.S. eventually blunts these decrease in cerebral pH, reducing ventilatory drive.

Sudden increase in p CO_2 retention causes acidemia that when severe (pH < 7,3) also contributes to pulmonary arterial vasoconstriction, reduced myocardial contractility, hyperkalemia, hypotension and cardiac irritability. Acutely raised Pa CO_2 (usually > 70 mm Hg) causes changes in sensorium ranging from subtile personality changes to markedly confusion and narcosis. Hypercapnea also cerebral vasodilation and increased C.S.F. pressure, a problem of major importance in the clinical setting of acute head injury. Acute acidemia secondary to raised Pa CO_2 is rapidly reversed by increasing alveolar ventilation to lower Pa CO_2.

Patients with chronic bronchitis and emphysema tend to fall into two clinical patterns, *pink puffers and blue bloaters*, although many show a spectrum between.

Pink puffers are thin with marked chest hyperinflation and are often very breathless: they have **type I respiratory failure** with modest hypoxemia with no carbon dioxide retention. Characteristically they do not develop pulmonaryhypertention and right ventricular hypertrophy, nor do they develop secondary polycythemia. In contrast, blue bloaters, with **type II respiratory failure**, have more marked central cyanosis, again with chest hyperinflation, but may not be so breathless. However, they may also have secondary polycythemia, with a raised jugular venous pressure and ankle edema.

In **sleep hypoxemia** arterial oxygen tension and saturation fall transiently, particularly during "rapid eye movement" sleeps. In the "sleep apnea syndrome" the upper airway transiently obstructs for more than ten seconds many times in each hour of sleep, air flow then ceasing at the nose and mouth despite continued inspiratory efforts. The arterial oxygen saturation falls recurently in each apneic episode. Obstructive sleep apnea may affect 1 - 10% of the population, and must be suspected in snorers, either obese or of normal weight, who have daytime sleepiness.

4. DISEASES ASSOCIATED WITH RESPIRATORY FAILURE

There are 3 pathophysiologic categories associated with respiratory failure:

1. those manifested by airways obstruction
2. those largely affecting the lung parenchyma but not the bronchi
3. those with primary ventilatory pump failure caused either by primary dysfunction of the respiratory center, by dysfunction of the ventilatory neuro-muscular apparatus, or by abnormalities of skeletal structures of the chest that prevent effective transmission of respiratory muscle forces.

Pathophysiologic changes in airway obstruction

Diseases in this category induce an abnormally high resistance to air flow due to retained airway secretions, bronchial mucosal edema, bronchial smooth muscle spasm or structural weakness of bronchial wall supports. The high resistance to air flow can affect alveolar gas exchange by disturbing the disturbution of ventilation to various parts of the lung with differing regional perfusion by mixed venous blood. High effort is required to produce the necessary pressure differences between the mouth and alveoli during expiration and inspiration.

The characteristic in lung volumes and ventilatory tests in intrathoracic airways obstruction are:

- reduced vital capacity (VC)
- increased residual volume (RV) and functional residual capacity (FRC) though total lung capacity (TLC) may be normal or increased

- reduced maximal voluntary ventilation, forced expiratory volume in one second (FEV 1) and air flow rates.

Pathophysiologic changes in diffuse parenchimal infiltration or edema

These diseases produce a pattern of physiological abnormality that is strikingly different from that in airways obstruction. All lung volumes, including RV, FRC, VC and TLC are reduced. Although forced expiratory flow rates (e. g. FEV1) are also diminished, the observed reductions are proportionate to the reductions in PLC and VC. Pa CO2 is usually normal and often below normal because of hyperventilation and almost never raised unless the patient is acutely decompensated. Pa O2, however, is mildly to moderately decreased both at rest and more markedly during exercise. In addition to V / Q inbalance, there is impaired diffusion of O2 from alveoli to pulmonary capillaries. This diffusion limitation is caused mainly by decreased total surface area for gas exchange, and to some extent by a structurally abnormal alveolar - capillary interface. Lung diffusion capacity for carbon monoxide (DL(CO)) is caracteristically decreased at rest and during exercise.

Unlike in obstructive lung diseases, the major mechanical abnormality is increased lung stiffness (decreased compliance). Worthened thoracic compliance may be the result of a diminished number of ventilated units (e. g. acute cardiac edema) or the result of increased tissue elastic recoil forces (e. g. interstitial fibrosis). Ventilatory drive is usually increased, frequently causing tachypnea and hyperventilation, either associated hypocapnea. Decreased lung compliance, increased ventilatory drive and hypoxemia all contribute to dyspnea, the outstanding symptom in this group of diseases.

Pathophysiologic changes in alveolar hypoventilation without primary broncho-pulmonary disease

When alveolar hypoventilation occurs in the absence of intrinsic lung or structural chest wall disease, Pa CO_2 is raised and Pa O_2 decreased.

The pathologic basis of the alveolar hypoventilation in the presence of normal lung structure varies from weakness or paralysis of the ventilatory muscles (e. g. in myasthenia gravis, infectious polyneuritis) to acquired or congenital damage to the medulary respiratory center. In most cases, lung compliance and airway resistance are unpaired or only mildly abnormal, and voluntary hypervetilation usually improves blood gas composition. In massive obesity, ventilatory drive may be diminished, owing primarily to chronic loading of the respiratory musculature, secondary to reduced chest wall compliance.

Table 11 - Causes of respiratory failure:

Pathogenesis	Disorder
Airways obstruction	Chronic bronchitis, emphysema, diffuse bronchiectasis, chystic fibrosis, asthma, bronchiolitis
Abnormal pulmonary interstitium	Sarcoidosis, pneumoconiosis, progressive systemic sclerosis, fibrosing alveolitis, idiopathic pulmonary fibrosis, drug sensitivity (hydralasine), disseminated carcinoma and Hodgkin's and non Hodgkin's lymphoma, radiation, histyocitosis
Alveolar hypoventilation without primary bronchopulmonary disease	Functional: sleep apnea, metabolic alkalosis Anatomic: abnormal respiratory center, abnormal chest cage (kyphoscoliosis) Disordered neuromuscular function: myasthenia gravis, infectious polyneuritis, muscular dystrophy, poliomyelitis Obesity, hypothyroidism

PATHOPHYSIOLOGY OF DYSPNEA

Definition of dyspnea: an unpleasant sensation of difficulty in breathing. Dyspnea is a symptom, not a sign, and is one of several sensation that a patient may describe.

A healthy person wil note the increased ventilation required during exercise, but will not interpret it as being particularly unpleasant unless taken to an extreme. A normal person at high altitude will be aware of a similar disproportionately large increase in ventilation resulting from exertion, and wil find it limiting but usually not otherwise unpleasant.

Other sensations related to breathing include awareness of increased muscular effort required to expand the chest during inspiration, increased effort required to expel air from the lungs, senstion of fatigue from the respiratory muscles, awarness of delay in air living the lungs during expiration or the unconfortable sensation that an inspiration is urgently needed before expiration is completed.

Afferent impulses to the brain that generate the sensation of dyspnea come from many different sites. Some come from the lungs; other seem to originate in the articulations of the rib cage and in the respiratory muscles including the diaphragm. Peripheral and central chemoreceptors provide part of the sensory input that appears to be involved in dyspnea, either directly or indirectly, and other visceral, neural and emotional stimuli may also participate.

TYPES OF DYSPNEA

1. Physiologic. The most common type of breathlessnes (dyspnea) is associated with physical exercise; ventilation is increased and maintained through an augementated respiratory stimulus provided by metabolic and other undefined factors. Dyspnea is also common during acute hypoxia, as at high altitude, where the increased respiratory stimulus is in part the effect of arterial hypoxemia on the carotid bodies. Dyspnea is also evoked by breathing high CO_2 concentrations in a closed

space. Dyspnea in this situation is similar to that brought on by exercise, and is primarily an awarness of increased ventilation. Increased CO_2 produces different sensations from reduced O_2 in the inspired gas. Hypoxemia is a much weaker stimulus to increased ventilation than is hypercapnea, and hypoxemia may produce other effects: confusion, a vague unpleasant sensation that is hard to define, or even unconsciouness.

2. Pulmonary. The two major pulmonary causes of dyspnea are a restrictive deffect with low compliance of the lung or chest wall and an obstructive deffect with increased resistance to air flow. Patients with restrictiv dyspnea (e. g. due to pulmonary fibrosis or chest deformities) are usually confortable at rest but become intensely dyspneic when exertion causes pulmonary ventilation to approach their greatly limited breathing capacity. In obstructive dyspnea (e. g. as in obstructive emphysema or asthma), increased ventilytory effort induces dyspnea even at rest, and breathing is labored and retarded, especially during expiration.

3. Cardiac. On early stages of heart failure, cardiac output falls to keep pace with increased metabolic need during exercise. Respiratory drive therefore is incresed largely because of tissue and cerebral acidosis, and the patient hyperventilates. Various reflex factors, including stretch receptors in the lungs may also contribute to hyperventilation.

In later stages of heart failure, the lungs are congested and edematous, the ventilatory capacity of the stiff lung is reduced, and ventilatory effort is increased. Reflex factors, particularly the juxtacapillary (*J*) receptors in the alveolar-capillary septa, contribute to the inordinate increase in pulmonary ventilation. Non-cardiogenic pulmonary edema or adult respiratory distress syndrome will produce a similar clinical picture by similar mechanisms, but more acutely.

4. Circulatory. Air hunger (acute dyspnea occuring in terminal stages of exanguinative hemorrhage) is a grave sign calling for immediate transfusion . Dyspnea also occurs with chronic anemia, coming on only during exertion, unless the anemia is extreme.

5. Chemical. Diabetic acidosis (blood pH 7,2 to 6,95) induces a distructive pattern of slow, deep respirations (Kussmaul breathing). However, because the breathing capacity is well preserved, the patient rarely complains of dyspnea. In contrast, the uremic patient may complain of dyspnea because of severe panting brought about by a combination of acidosis, heart failure, pulmonary edema, and uremia.

6. Central. Cerebral lesions (e. g. hemorrhage) are often associated with intense hyperventilation that is sometimes noisy and stertorous. Occasionnaly unpredictably irregular periods of apnea alternate with periods in which 4 or 5 breaths of similar depth are taken (Biot's respiration). Hyperventilation is also frequently seen after

head injury. Decreased $PaCO_2$ causes reflex CNS vasoconstriction with reduced cerebral perfusion leading to a beneficial secondary decrease in intracranial pressure.

7. **Psychogenic.** Hysterical types of overbreathing are common. In one type, continnous hyperventilation sometimes leads to acute alkalosis; positive Trousseau and Chvostek signs may result from lowered serum calcium ion levels.

PATHOPHYSIOLOGY OF CYANOSIS

Cyanosis is a bluish coloration of the skin and mucous membranes that develops as a result of an increase in the absolute amount of reduced hemoglobin (hemoglobin not united with oxygen). It may be a sign of respiratory insuffiency, although this is a highly unreliable indication. There are two types of cyanosis: central and peripheral.

Central cyanosis resulting from insufficient oxygenation of hemoglobin in the lungs is mostly observed on the face, hips and ear lobes and under the tongue. Central cyanosis is present in the warm mucous membranes as well in cooler skin.

Cyanosis is generally not detected until absolute amount of reduced hemoglobin is 5 g / 100 ml or more in a person with normal hemoglobin concentration. The normal amount of reduced hemoglobin in the capillary bed is 2,5 g / 100 ml. In the person with a normal hemoglobin concentration, oxygen saturation is about 75% and Pa O2 is 50 mm Hg or less when cyanosis is first detected. Anemic patients (low hemoglobin concentration) may never become cyanotic, even though they have severe tissue hypoxia, because the absolute amount of reduced hemoglobin is not likely to reach 5 g / 100 ml. On the other hand, a person with polycytemia (high hemoglobin concentration) can easily have 5 g / 100 ml of reduced hemoglobin when there is only mild hypoxia.

In conclusion, cyanosis is less readily detectable if anemia is present, and more readily seen in polycytemia. Other factors that make cyanosis difficult to recognise are variations in the skin thickness, pigmentation and lighting conditions.

Pulmonary causes of central cyanosis are those that can cause arterial hypoxemia: intrapulmonary shunting, impaired diffusion, inadequate alveolar ventilation and mismatching on ventilation and perfusion. Presence of central cyanosis will always be an indication for arterial blood gas measurement and diagnostic efforts to determine whether the cyanosis is pulmonary in origin or results from cardiac disease or cardiovascular anomalies.

In addition to cyanosis caused by respiratory insufficiency (central cyanosis) **peripheral cyanosis** occurs when severely reduced blood flow causes great reduction in the venous saturation, thereby turning an area blue. Peripheral cyanosis may result from cardiac insufficiency, obstruction of blood flow, or vasoconstriction due to cold temperatures.

Cyanosis may also be produced by small amounts of circulating methemoglobin and by even smaller amounts of sulfhemoglobin although these causes are uncommon.

II.1.2. PATHOPHYSIOLOGY OF LUNG DISEASES

Diffuse pulmonary diseases can be classified into two categories, based on fundamental differences in the pulmonary function tests:

I.Obstructive lung diseases, also called airway diseases, characterized by an increase in resistance to air flow due to partial or complete obstruction at any level.

The major obstructive disorders, excluding tumor or inhalation of foreign body, are:

1. Asthma
2. Emphysema
3. Chronic bronchitis

Narrowing of the airways or extensive distruction of the alveolar septa result in diminution of lung elasticity and collapse of the airways during exhalation, with secondary air trapping in the distal lung.

Laboratory tests show:

- decreased respiratory flow rate: forced expiratory volume (F.E.V.1) levels are reduced, as are the FEV1 / VC
- residual volume is increased because of air trapping as a correlative to diminished vital capacity

II. Restrictive diseases, include all of the lung diseases in which the main pathophysiology is a disturbance of the diffusion of gases.

Restrictive diseases occur in two general conditions:

1. Extrapulmonary disorders, which affect the ability of the chest wall:
   - severe obesity
   - neuromuscular disorders affecting the respiratory muscles
   - elevation of the diaphragm due to abdominal masses or ascites
   - deformities of the chest wall (kyphoskoliosis)
2. Acute or chronic interstitial lung diseases and pleural diseases:
   - pneumonias
   - neoplasm
   - familiar idiopathic or acquired pulmonary fibrosis
   - multiple pulmonary emboly
   - pleural effusion or pneumothorax

Fibrotic reaction of the alveolar septa, thickning of the alveolar- capillary membrane, distruction of the lung parenchyma and decreased lung compliance because of pleural diseases lead to increased resistance during inspiration and increased of elastic recoil with a rapid exhalation.

Laboratory tests show:

- vital capacity and total lung capacity are reduced
- expiratory flow is normal
- FEV / VC is normal: this is one of the most distinguishing features differentiating restrictive lung disease from obstructive lung disease

ASTHMA

It is characterised by **episodic, reversible** bronchoconstriction resulting from **increased responsiveness** of the tracheo-bronchial tree to various stimuli. Airway hyperresponsiveness is defined as an exaggerated bronchoconstrictor response to stimuli that have little or no effect in nonasthmatic patients.

Clinically, asthma is manifested by:

- dyspnea
- cough
- wheezing (soft whistling sound during expiration)

Asthma is a heterogenous disease triggered by a variety of agents. There are two major categories of asthma based on the presence or absence of an underlying immune mechanism:

1. Extrinsec asthma, in which the asthmatic episode is initiated by a type I hypersensitivity reaction induced by exposure to an extrinsic antigen. Thus, allergic asthma is dependent on an IgE response controlled by T- and B lymphocytes and activated by the interaction of antigen with mast-cell bound IgE.

Two types of extrinsic asthma are recognized:

- atopic asthma
- occupational asthma: inhaled irritants

The onset of atopic asthma is usually in the first decade of life and it is associated with other allergic manifestations (rinitis, urticaria) and a family history of allergic diseases

2. Intrinsic asthma, in which the triggering mechanisms are non-immune. In this form, a number of stimuli can initiate brochospasm, including:
   - pulmonary infections, especially those caused by viruses
   - cold
   - aspirin

- physiological stress
- exercise

PATHOPHYSIOLOGY

Current studies show that bronchial asthma is an inflammatory condition.

Airway obstruction in asthma is due to a combination of factors that include:

- spasm of the smooth muscles of the bronchiolas
- oedema of the mucosae
- increased mucus secretion
- infiltration of the mucosa with different types of leukocytes: T- helper lymphocytes subtype 2, eosinophils, mast cells, neutrophils
- injury and descuamation of the epithelium
- in chronic asthma there is thickning of the airway wall due to hypertrophy and hyperplasia of the mucus- secreting glands and secretory cells, hyperplasia of airway smooth muscle and deposition of submucosal collagen.

The common dominator underlying all forms of asthma is increased airway reactivity to a variety of stimuli, also called **bronchial hyperresponsiveness.**

Research on the pathophysiology of asthma has focused on two directions:

1. Inflammation

In allergic asthma, attacks of bronchoconstriction demonstrate three phases:

- **The immediate reaction** is triggered by antigens which bind the IgE on mast-cells in the airways. Mast cell release mediators which cause bronchoconstriction and open tight junctions between epithelial cells. Antigen can then enter into the mucosa to activate mucosal mast-cells and eosinophils and stimulate parasympathetic nervous system to cause severe bronchoconstriction.
- **The late phase**, which is dominated by additional recruitement of leukocytes (basophils, neutrophils and eosinophils) and platelets
- **The chronic phase**, which is characterised by deposition of collagen, hyperplasia of the smooth muscle cells and thickning of the airway wall

The accepted explanation for bronchoconstriction in acute episode is release of bioactive mediators:

2. Acetylcholine: it results from parasympathetic end nerves and acts on muscarinic receptors subtype 3 (M3)
3. Adenosine: it results from rapid extracellular metabolism of ATP and acts on adenosine receptor
4. Histamine: mast cells represent the major source ; it acts on H1 receptors

5. Kinines: potentially significant bronchoconstrictor, it results from the cleavage of plasma precursors by the enzyme kalikrein, released by mast cells
6. Leukotrienes:
   - LT C4, D4 and E4 are released by mast cells, macrophages and eosinophils; they are bronchoconstrictors
   - LT B4 is released by neutrophils; it is a chemoattractant
7. Neuropeptides: substance P and neurokinin A act on NK1 and NK2 receptors (later is enhanced in asthmatic patients)
8. Nitricoxide: produced enzymatically by epithelial and inflammatory cells; bronchodilator but the peroxinitrit radical(formed by the combination of nitricoxide with superoxide) causes damages of the bronchial epithelium
9. Platelet activating factor (PAF): phospholipid released by mast cells and eosiniphils; it causes airways hyperresponsiveness

Clinical trials with leukotrien or PAF receptor antagonists show that they might be effective in either exercise- induced or allergic asthma.

One of the most important of these cells is the **eosinophil**: when activated, the eosinophil can produce leukotrien C4 and PAF. Degranulation of eosinophils can release the **major basic protein** and the **eosinophil kationic protein** into the airways, thus causing cilia to stop beating and disrupting mucosal integrity with exfoliation of cells into the bronchial lumen.

*2. **Neurogenic mechanisms***

It should so be mentioned that bronchial **hyperresponsiveness** has also been ascribed to some fundamental defect in the **autonomic regulation**. Speculations about neurogenic influences on the pathogenesis of asthma led to the following theories:

a. the reduced activity of the β-adrenergic pathway. Perhaps there is a hereditary or acquired reduced activity of β2-adrenergic receptors. Normally, activation of β2-receptors stimulates the cAMP formation resulting in bronchial smooth muscle relaxation and inhibition of mediator release.
b. cholinergic pathway normally causes airway obstruction
c. non-adrenergic, non-cholinergic pathway involves **neuropeptides** release (such as substance P or neurokinin A) from sensory nerves by an axon reflex triggered by inhalation of irritant substances (ozone, nitrogen dyoxyde).

The pathophysiologic changes described above lead to airways obstruction. The consequence of the airway obstruction is an increased resistance to airflow, which is manifested by decreased expiratory flow rates and diminution of the lung elastic

recoil . The expiratory phase of respiration becomes active as the patient tries to force air from the lungs.

The respiratory rate is usually rapid during an acute asthmatic attack. This tachypnea is driven by abnormalities in arterial blood gas composition (hypoxemia) but rather by stimulation of intrapulmonary receptors with subsequent effects on central respiratory centers. One consequence of airway narrowing combined with these rapid airflow rates is a heightened mechanical load of the ventilatory pump (increased consumption of oxygen, also called work of breathing).

The patchy nature of airway narrowing results in a maldistribution of ventilation relative to pulmonary perfusion. There are nonventilated but perfused alveoli , whith a V/ Q ratio of less than unity. The net effect is to induce arterial hypoxemia. In addition, the hyperpnea of asthma is reflected as hyperventilation and a low arterial partial pressure of carbon dioxide and respiratory alkalosis.

Pulmonary function tests show that forced expiratory volume, permeability index and functional residual capacity are all reduced in asthma. Arterial hypoxemia and hypocapnia, respiratory alkalosis and compensatory metabolic acidemia are the rules.

CHRONIC BRONCHTIS (CB)

The diagnosis of chronic bronchitis is made on clinical grounds. It is defined as a persistent productive cough for at least three consecutive months it at least two consecutive years.

CB is a condition associated with prolonged exposure to bronchial irritants (cigarette smoking) and it is accompanied by mucus secretion, hypertrophy of mucous glands and damages of the mucosal epithelial cells.

These structural changes result in **airway hyperresponsiveness** and **intermitent episodes of bronchoconstriction.**

EMPHYSEMA

It is characterized by permanent enlargement of the air spaces distal to the terminal bronchioles accompanied by destruction of their walls with secondary **loose** of elastic fibers and capillaries.

The basic lesion of emphysema is believed to result from:

- airway obstruction
- imbalance between the proteolytic enzymes and antiproteases in the lower respiratory tract

This protease- antiprotease hypothesis is based on the observation that patients with a genetic deficiency of the antiprotease α-1 antitripsine have a tendency to

develop emphysema. The protease inhibitor, or **PI**, phenotype of the subject determines the trypsin inhibitory capacity of the serum. Two M genes (Pi MM phenotype) are present in normal individuals. When only Z genes are present (Pi ZZ phenotype), serum α1- antitripsine levels are severely reduced.

α-1 antitripsine is normally present in the serum and tissue fluids and it is a major inhibitor of elastase.

The following sequence is postulated:

- neutrophils - the principal source of elastase - is normally sequestered in capillaries
- any agent (cigarette smoking) increases the elastolytic activity through either increasing the number of neutrophils in the alveoli ot the release of their elastase.
- tissue-lung destruction

Emphysema is classified **according to the pattern of involvement** of the gas-exchanging units (acini) of the lung:

1. Centriacinar emphysema: the destruction is limited to the respiratory bronchiole and alveolar ducts, with relatively less change peripherally in the acinus; it is the most common form of emphysema in patients with chronic airflow obstruction caused by smoking.
2. Panacinar emphysema involves both the central and peripheral portion of the acinus; it is generally associated with antiprotease deficiency.

Destruction of the alveolar wall results in:

- **loss of radial traction** on airways and increase in airway resistance with secondary diminution in maximal expiratory flow rate
- **loss of elastic properties** of the lung. Thus, the work of expiration (the O2 utilisation by the respiratory muscles) is increased.

Disapearance of the elastic fibers reduces lung elastic recoil, which permits excessive airway collapse upon expiration and leads to irreversible airflow obstruction.

Persistent reduction in flow expiratory rates is one of the most typical finding in emphysema. The residual volume and the ratio of residual volume to total lung capacity, are elevated. When the diffusing capacity is very depressed (due to extensive loss of the alveolar – capillary membrane) and the total lung capacity is clearly increased, emphysema is likely to be extensive. Ventilation- perfusion mismatch and nonuniformity of ventilation, arterial hypoxemia and shunting respiration are typical findings.

CHRONIC OBSTRUCTIVE PULMONARY DISEASES (COPD)

COPD refers to **generalized persistent airways obstruction**, due to an increased resistance to air flow during expiration resulting from:

- obliteration of airways in all clinical forms of chronic bronchitis
- reduced elastic properties in emphysema

Patients with chronic airway diseases have some combination of these diseases. Thus, COPD has two major types:

1. Predominant emphysematous:
   - dyspnea is the first symptom
   - cough after dyspnea, with scanty sputum
   - hypoxemia and hypercapnia do not occur until terminal stage
   - cyanosis is absent, thus the patient is also called "pink puffer"
2. Predominant bronchitis
   - cough with copious and purulent sputum is the first symptom
   - hypoxemia and hypercapnia are recurrent events and they are associated with respiratory infections
   - cyanosis is present, thus the patient is also called "blue bloater"

Not only chronic bronchitis but also lung emphysema leads to cor pulmonale.

Cor pulmonale is defined as the right ventricular enlargement due to hypoxic-induced pulmonary hypertension.

Pulmonary hypertension is caused by the following mechanisms:

- a reduction of the pulmonary capillaries because of the destruction of alveolar wall
- a constriction of the pulmonary vessels in response to alveolar hypoxia (von Euler's reflex) or hypoxemia (Cournard's reflex)

Persistent hypoxia may cause hypertrophy and sclerosis of the arterial wall resulting in permanent (irreversible) pulmonary hypertension. Pulmonary hypertension refractory to oxygen therapy enhances the right ventricle afterload and causes right ventricular hypertrophy. The state is called compensated cor pulmonale.

Polycytemia and increased blood viscosity (due to the stimulation of bone marrow erythrocytosis via erithropoetin) causes an enhance of right ventricular preload.

Hypercapnia, which is a main characteristic of severe cases, leads to respiratory acidosis. Renal compensation consists of tubular reabsorbtion of bicarbonate in order to normalise acid- base balance. This compensatory mechanism lead to hypervolemia and thus to increased right ventricular preload and right ventricular failure.

ACUTE PULMONARY OEDEMA (APO)

It is the most important form of local oedema associated with liquid accumulation in the interstitial tissue and pulmonary alveoli.

The passage of fluid through the alveolar-capillary membrane depends upon Starling's laws that define two forces:

1. The pressure tending to move liquid **out** of the vessels is composed of:
   - the mean intracapillary pressure (Pc)
   - the oncotic pressure of the interstitial tissue
2. The pressure tending to move liquid **back into** the vessels is made of:
   - mean interstitial liquid pressure
   - oncotic pressure of the plasma

Lymphatic flow can increase in the case of imbalance of forces and result in no net accumulation of interstitial liquid.

There are two major types of APO:

1. Cardiogenic pulmonary oedema

Elevation in intracapillary pressure, in left ventricular failure or mitral stenosis results initially in **engorgement** of the pulmonary capillaries. The lung becomes less compliant with secondary dyspnea.

This effect leads to liquid filtration that **exceeds** clearance capability by the lymphatics, and liquid accumulates in the interstitial spaces of the lung.

Persistent elevation of intracapillary pressure leads to alveolar flooding. At this point, alveolar oedema is present. Gas exchange is severely compromised with hypoxia hypocapnia and pulmonary alkalosis. Severe cases are associated with respiratory failure type II: hypoxia,hypercapnea and respiratory acidosis.

2. *Non-cardiogenic pulmonary oedema* involves the following mechanisms:
   a. Decreased plasma oncotic pressure in hypoalbuminemia
   b. Increased negativity of interstitial pressure:
      - rapid removal of pneumothorax
      - negative intrapleural pressure because of acute airway obstruction (attack of asthma)
   c. Adult respiratory distress syndrome (ARDS)
   d. lymphatic blockade (secondary to lymphatic metastases of different malignancies)
   e. Exposure to high altitude in association with severe physical stress: increased output of the right ventricle with engorgement of the pulmonary capillaries because of exercise combined with hypoxic pulmonary vasoconstriction

   f. Neurogenic pulmonary oedema in patients with central nervous system disorders: massive cathecolamines levels leading to peripheral vasoconstriction and shifts of blood to the pulmonary circulation.

Adult respiratory distress syndrom (ARDS) is defined as a noncardiogenic pulmonary oedema caused by stimuli which seems to be an inflammatory response to distant or local tissue injury (table 1).

Table 12 - Adult respiratory distress syndrome. Etiology

1. Aspiration: • Gastric contents • Salt water	Direct damages or inflammation
2. Drug overdose or allergic reaction: • Aspirin • Heroin	Oxidative injuries
3. Infections: • Sepsis • Pneumonia	Inflammation: - cytokines - bioactive mediators - cascade activation of complement coagulation or kinines - proteases - reactive oxygen species
4. Inhalation of gases: • Oxygen • Smoke • Corrosive chemicals	Direct damages Oxidative injuries
5. Metabolic disorders: • Pancreatitis • Uremia	Direct damages Vascular congestion Activation of bradikinin cascade
6. Shock (uncommon in cardiogenic or hypovolemic shock)	Tumor necrosis factor
7. Pulmonary embolism	
8. Central nervous system: • Seizures • Intracranial hypertension	

The initial insult causes injury of the alveolar capillary membrane and a local inflammation, involving release of cytokines, mediators from cell membrane (arachidonic acid and platelet activating factor), and activation of a number of cascades (complement, coagulation and kinin). Neutrophils activating and adhering to endothelial cells with release of oxygen free radicals and proteases may contribute to endothelial damage, with a subsequent sequence of events: diffuse alveolar infiltrates, respiratory distress, hypoxemia and respiratory failure.

Table 13 - Differential diagnosis between cardiogenic and noncardiogenic pulmonary edema

1. Prior history: - age less than 60 - no history of heart disease - normal fluid balance	- age more than 60 - prior history of heart disease - abnormal fluid balance: heart failure, hypertension or hyperhydration
2. Physical examination: - flat neck veins - absence of edema	- left ventricular enlargement - gallop, murmurs - enlargement of the jugurar veins - peripheral edema
3. ECG: - synus tachycardia	- left ventricular hypertrophy
1. Chest radiography - normal heart size - peripheral distribution of the infiltrates - vascular pedicle less than 48 mm	- cardiomegaly - central or basilar infiltrates - vascular pedicle more than 53mm - interstitial edema (Kerley lines)
2. Hemodinamic measurements: - pulmonary artery pressure less than 15 mm Hg - cardiac index more than 3.5 L/ min/ m2	- pulmonary artery pressure more than 18 mmHg - cardiac index less than 3.5 L/ min/ mm2
Noncardiogenic APO	Cardiogenic APO

PATHOPHYSIOLOGY OF PLEURAL DISORDERS

Normally, only a thin layer of serous fluid separates the visceral and parietal layers of the pleural cavity.

Pleural effusion (PE) refers to a collection of fluid in the pleural cavity.

Like oedema, PE occurs when the rate of fluid formation exceeds the rate of its removal. There are four mechanisms:

- increased capillary pressureas in comgestive heart failure
- increased capillary permeability which occurs in inflammatory conditions of pleura
- decreased coloidal osmotic pressure (hypoalbuminemia occuring in liver cirrhosis and nephrotic syndrome)
- impaired lymphatic drainage of the pleural space: mediastinal carcinoma.

PE may involve the presence of a transsudate or exudate:

- transsudate equals hydrothorax, non-inflammatory collections of serous fluids. The most common cause is congestive heart failure

Characteristic: protein contents less than 3 g / dl.

- exudate equals inflammatory collections in infections, pulmonary infarction, cancers.

Characteristic: protein contents more than 3 g / dl.

Empyema refers to the presence of pus in the pleural cavity.

Chylothorax refers to the presence of chyle in the thoracic cavity resulting from trauma, inflammation or malignant infiltration obstructing chyle transport from the thoracic duct into the central circulation.

Hemothorax is the presence of blood in the thoracic cavity resulting from:

- chest injury
- complication of the chest injury
- malignancies
- rupture of an aortic aneurysm in the pleural cavity

Manifestations of PE:

- a decrease in vital capacity resulting in dyspnea
- a mediastinal shift toward the contralateral side with a decrease of contralateral lung capacity too resulting in respiratory failure
- diminished breath sounds
- pleuretic pain

Pneumothorax refers to an accumulation or complete collapse of the lung.

1. Spontaneous pneumothorax
2. Secondary pneumothorax - air enters the pleural space as the result of injury to the chest wall, respiratory structures or oesophagus.

3. Tension pneumothorax - the pressure within the pleural space is greater than the atmospheric pressure during the entire respiratory cycle. It occurs when injury permitts air to enter but not leave the pleural space so that the lesion acts as an overway valve, resulting in:
   - a rapid increase in pressure within the chest
   - a compression atelectasis of the lung
   - a shift in the mediastinum to the opposite side of the chest
   - atelectasis of the controlateral lung
   - compression of the vena cava with the impairment of the venous return to the heart leading to decreased cardiac output.

II.2. Pathophysiology of cardiovascular system

II.2.1. Pathophysiology of atherosclerosis

Arteriosclerosis is the generic term for three patterns of vascular disease, all of which cause thickening and inelasticity of arteries.

The dominant pattern is **atherosclerosis** (AS), disease of large and medium arteries, characterized by the formation of intimal fibrofatty plaques, that often have a central core rich in lipids, hence the term "atherosclerosis" from the Greek stem others meaning "gruel of poridge".

The **second** form of arteriosclerosis is the rather trivial **Monckberg's** medial calcific, sclerosis, characterized by calcification in the media of muscular arteries, in persons usually over the age of 50.

The **third pattern** is **ateriolosclerosis**, disease of small arteries and arterioles; this sclerosis is most often associated with hypertension and diabetes mellitus.

Although any artery may be affected by AS, the major targets are the aorta and the coronary and cerebral arteries. Coronary atherosclerosis induces ischaemic heart disease (IHD) and when the arterial lesions are complicated by thrombosis, the most serious form of IHD, myocardial infarction (MI), which alone is responsible for 20% to 25% of all deaths in the United States. Atherothrombotic disease of cerebral vessels is the major cause of brain infarcts, so-called strokes, one of the commonest forms of neurologic disease. Were this not sufficient, atherosclerosis often produces critical ischaemia of the intestines and lower extremities, and it is a major cause of abdominal aortic aneurysms (abnormal dilatations) that sometimese rupture to produce massive fatal hemorrhage. The disease begins in the early childhood and progresses slowly over the decades. Thus, in some measure AS is a pediatric disease,

and if its toll is to be reduced, measures must be instituted early before it rears its ugly head and provokes one of its unfortunate consequences.

PREVALENCE AND EPIDEMIOLOGY

With its effects upon the brain, heart, kidneys, other vital organs, and extremities, vascular disease is the leading cause of morbidity and mortality in the USA and in most Western countries, with almost 1 million deaths in the USA in 1986 (twice as many as from cancer and 10 times those from accidents). Despite progress in prevention and treatnent of coronary artery disease (CAD) resulting in a 23,3% reduction in age-adjusted death cases between 1977 and 1987, atherosclerotic heart disease and stroke remain the number one killer.

The death rate from CAD among white men aged 25 to 34 is about 1/10.000; at age 55 to 64, it is nearly 1/100. This age relationship may be due to the time required for the lesions to develop or to the duration of exposure to risk factors. Between ages 35 and 44, the death rate from CAD among white men is 6,1 times that among women. In nonwhites, for unknown reasons, the sex differents is less apparent.

RISK FACTORS

The prevalence and severity of the disease, and therefore age when it is likely to cause tissue or organ injury, are related to a number of factors, some constitutional and therefore not modifiable, but others acquired and potentially controllable. The **constitutional factors** include age, sex, and familial background.

- **Age**. Age is a dominant influence. Although early lesions of AS appear in childhood, clinically significant disease, as judged by the death rates from IHD, rises with each decade, even in to advanced age. For example, from age 40 to 60 there is a greater than fivefold increase in the incidence of myocardial infarction. It is an exceptional adult in the United States who is older than 20 years and does not have at least mild AS.
- **Sex**. Other factors being equal, males are much more prone to AS than females. Females are more or less sheltered from advanced, disease-producing As until menopause, so myocardial infarction is uncommon in premenopausal women unless they are predisposed by diabetes or some unusual (possibly familial) form of hyperlipidemia or have severe hypertension. After menopause the protection slowly dwindles until the frequency of MI becomes the same in both sexes by the seventh to eighth decade of life. Between ages 35 and 55 years, white women have one fifth the mortality from IHD of white males.
- **Familial predisposition**. The is a well-defined familial predisposition to AS and to IHD. In some instances it relates to **familial clustering of other risk factors**, such as hypertension and diabetes. In other instances, it involves

well-defined hereditary **genetic derangements** in lipoprotein metabolism that result in excessively high blood lipid levels. The prototype of these conditions is familial hypercholesterolemia, but in addition there is a growing number of familial dyslipoproteinemias, most of which result from mutations that yield defective **apolipoproteins**. You may recall, these are proteins bound to the various blood lipid fractions, which have many functions, among them: activation or inhibition of particular enzymes, facilitating transmembrane transport of certain lipoproteins, and serving as ligands to high affinity cellular receptors that guide the lipoproteins to specific sites of catabolism.

There are **four major acquired risk factors** that are the least in some part amenable to control:

1. acquired hyperlipidemia;
2. hypertension;
3. cigarette smoking, and
4. diabetes (as well as a number of less important "soft risks").

1. **Hyperlipidemia** is virtually universally aknowledged to be a major factor for AS. Most of the evidence specifically implicates hypercholesterolemia, but hypertriglyceridemia may also play a role, although it is not as significant as hypercholesterolemia. You recall that the various classes of blood lipids are transported as lipoproteins complexed to specific apoproteins.

The major evidence implicated hypercholesterolemia in the genesis of AS includes the following:

- High-cholesterol diets can produce atherosclerotic plaques in rabbits, guinea pigs, dogs, and other nonhuman animals that are nearly identical to those observed in the human disease.
- The major lipids in atheromas (plaques) are cholesterol and cholesteryl esters derived from the plasma. Triglycerides and fatty acids are present in small amounts.
- Many large scale analyses (notably the Framingham study) have demonstrated a nearly linear correlation between the total plasma cholesterol or low-density lipoprotein (LDL) level and the severity of AS as judged by the mortality rate from IHD. The higher the total cholesterol level the greater the risk of symptomatic and fatal atherosclerotic disease.

No threshold clearly separates persons at risk from those free of risk, but in general, **atherosclerotic events** are very uncommon with total serum cholesterol levels below **150 mg/dl**. Hypertriglyceridemia, as manifested by elevated very-low density lipoprotein (VLDL) levels, is also associated with some increased risk, but the association is much weaker than for LDL.

- **Genetic or acquired disorders** (e.g., diabetes mellitus, hypothyroidism) that cause **hypercholesterolemia** lead to premature and rampant atherosclerosis; withness familial hypercholesterolemia, which in the homozygous state is often associated with myocardial infarction before age 20 years.
- When levels of serum cholesterol are lowered, there is substantial evidence in animals and suggestive evidence in humans that some (many) atherosclerotic plaques regress, or fail to progress, within months.

It is important at this point to emphasize the **inverse relationship** between simptomatic AS and the high-density lipoprotein (HDL) level. HDL participates in reverse transport of cholesterol and is believed to mobilize this lipid from cells and presumably from atherosclerotic plaques and transport it to the liver for excretion in the bile. **The higher the levels of HDL 3 and HDL 2 the lower the risk of IHD.** Hence the great interest in methods of lowering the serum LDL and raising the HDL level. A heavy dietary intake of saturated animal fat, including cholesterol-laden butter, other dietary products and eggs, rises the serum cholesterol level. Conversely, diets in which saturated fats are replaced by monounsaturated (e.g., olive oil) or polyunsaturated fats (e.g., fish, corn oil) lower the LDL level, but may concurrently modestly reduce the HDL level. In particular, the ω-3 polyunsaturated fatty acids from fish and fish oil have a well-defined hypolipidemic effect. Vegetarians and habitual fish eaters (e.g., Greenland Eskimos) with diet high in unsaturated fats relative to saturated hats have low levels of LDL and consumption of ethanol both rise the HDL level, whereas obesity and smoking lower it. Many more observations could be cited, but it suffices that blood cholesterol and LDL levels are major contributions to atherogenesis.

2. **Hypertension** is at all ahes a major risk factor for atherosclerosis and may well be more important than hypercholesterolemia after age 45. In the Framingham study, men aged 45 to 62 whose blood pressure exceeded 160/95 mm Hg had a more than fivefold greater risk of IHD that those with blood pressures of 140 or lower. The dyastolic level appears to be more important than the systolic.
3. **Smoking** is also a major risk factor and is thought to account for the recent increase in the incidence and severity of AS in women. When one or more packs of cigarettes are smoked per days for years, the death rate from IHD increases up to 200%. Cessation of smoking dramatically reduces this increased risk in time.
4. **Diabetes mellitus** induces hypercholesterolemia and a markedly increased predispozition to atherosclerosis. Other factors being equal, the incidence of myocardial infarction is twice as high in diabetics as in nondiabetics. There is also an increased risk of strokes and even more striking, perhaps, a

hundredfold increased risk of atherosclerosis-induced gangrene of the lower extremities. Indeed, in the absence of diabetes, atherosclerotic gangrene of the lower extremities is uncommon.

Other risk factors are sometimes called "soft risk factors because their impact on atherogenesis is less clearly defined and in some instances is controversial. There is substantial evidence than physical activity increases the serum level of HDL, having a protective effect against IHD, and conversely inactivity favors the development of AS. Moreover, physical activity appears to reduce the risk of sudden death, which is most often a consequence of IHD. Analogously, in the Framingham study, **being more than 30% overweight increases the mortality rate from IHD.** The risk appears to be mainly connected to weight gain in the abdominal region, in contrast to adiposity located mainly in the gluteal region or proximal extremities. Genetic metaabolic factors may determine this variable distribution of adiposity because with abdominal obesity there is frequently concomitant hypertriglyceridemia, impaired glucose tolerance, and hypertension, not seen with the other forms of obesity. Some of the other less significant ("softer") risk factors include type A personality behavior, hyperuricemia, and the use of former oral contraceptives, there have been claims of a direct association between coffee consumption and increased serum cholesterol levels, particularly the consumption coffee brewed by boiling. To the great relief of "coffeecholies", the drinking of filtered coffee is reported to have no effect on the blood lipids, removing the stigma from one of life's simpler but cherished pleasures.

In closing this discussion of risk factors it is important to note that **multiple factors impose more than an additive effect.** The Framingham study documented that when three risk factors were presented (hyperlipidemia, hypertension, and smoking), the heart attack rate was **seven times** greater than where none has present. Two risk factors increased the risk **fourfold.** However, the converse is equally important: AS may develop in the absence of any apparent risk factors , so even those who live "the prudent life" and have no genetic predispositions are not immune to this killer disease.

PATHOGENESIS

Undestandably, the commanding importance of AS has stimulated enormous efforts to discover its cause. A mountain of evidence has accumulated, but unfortunately it is strewn with claims and counterclaims and has led to numerous **pathogenic theories.** Comments will be restricted to only three of these theories.

I. Favored today and receiving the greatest attention is the **endothelial dysfunction hypothesis.** It best accommodates the various risk factors discussed; central to this thesis are the following features:

- The development of focal areas of chronic endothelial injury, usually very subtle, with resulting increased endothelial permeability or other evidence of endothelial dysfunction.
- Increased imbibition (insudation) of lipoproteins, mainly LDL or modified LDL (oxidatin) with its high content of cholesterol, and also VLDL.
- A series of cellular interactions in these foci of injury involving endothelial cells, monocytes/macrophages, T lymphocytes, and smooth muscle cells of intimal or medial origin.
- Proliferation of smooth muscle cells in the intima with the formation of connective tissue by the smooth muscle cells.

Endothelial injury has long been considered as a prerequisite for ATS plaque formation.

Experimental and clinical studies have proved that during lesion development the endothelium is morfologically INTACT, but the phenotype is changed to an activated state.

Activated state and dysfunction favours the chronic inflammatory process leading to ATS disease.

Endothelium is involved in ATS in several manners:

1. Subendothelial accumulation of atherogenic lipoproteins, through the barrier properties of endothelium.
2. Intimal accommulation of macrophages through recruitment and adhesion of monocyte, when end cells are activated.
3. Vasospasm, when its vasodilatatory properties are altered.
4. Thrombus formation, when the endothelium is eroded.

A. Chronic or repeated endothelial injury is the key-stone of the response-to-injury hypothesis.

Endothelial cells show different functions.

1. they mediate the passage of nutrients and other substances from blood to tissues, acting as a selective permeability barrier and a blood compatible container.
2. provide a non-thrombogenic surface to which platelets and other blood cells fail to adhere.
3. maintain a potent lumen by growing as a single-cells layer tightly adherent to the basement membrane of the vessel wall. Endothelial cells are now recognized as having a variety of synthetic and metabolic capabilities.

Although endothelial denuding injuries will certainly initiate atherosclerotic changes in experimental animals, the naturally occuring disease of human beings with some form of non-denuding, subtle injury. Circulating endotoxins, anoxia, carbon monoxide or other products derived from cigarette smoke, viruses, and specific endotheliotoxins such as homocysteine (accounting for the premature and severe

atherosclerosis of homocysteinurics) could be involved, but thought to be much more likely are hemodynamic disturbances (shear stress, turbulent flow) and adverse effects of hypercholesterolemia, perhaps acting in concert.

Shear stress and turbulent flow have been shown experimentally to increase endothelial permeability, increase cell turn-over and to enhance receptor-mediated LDL endocytosis.

The complex geometry of the arterial system, with its twists and turns and branching, could give rise to turbulent flow patterns with variable levels of shear stress capable of causing focal areas of endothelial injury. In support of this notion is a well-defined tendency for plaques to occur at mouths of existing vessels, branch points, and along the posterior wall of the descending and abdominal aorta which is caught between the anvil of the vertebral column and the hammer of the arterial pulse. Whether hemodynamic stress can account for the widespread involvement often seen in the aorta with advanced disease remains to be established.

B. The possibility that chronic hyperlipidemia **(the lipid hypothesis)**, and particulary hypercholesterolemia, may itself initiate endothelial injury has enticed many investigators. Much evidence suggests that hypercholesterolemia has a variety of adverse effects.

1. Hypercholesterolemia increases the cholesterol/phospholipid ratio of endothelial cell membranes, rendering them more rigid and less able to maintain their normal intercellular associations, potentially increasing permeability and in effect causing a subtle for of endothelial injury.
2. It favors the adherence of monocytes and lymphocytes to the focus of injury, in part owing to the stimulation of endothelial cell synthesis of adhesion molecules.
3. It induces changes in platelet membrane composition, leading to activation and increased adhesiveness of platelets.
4. With chronic hyperlipidemia, lipoproteins accumulate within the intima at sites of endothelial injury or dysfunction. Although significant amounts may enter the arterial wall, there is some concomitant efflux, perhaps mediated by HDL.
5. Most important, it provides **the opportunity to oxidation of lipoproteins,** yielding modified LDL.

Oxidative modification of LDL is currently thought to be an important aspect of the atherogenic process. It is proposed that LDL in the microenvironment of interadherent monocytes and endothelial cells is exposed to free radicals generated by these activated cells. Oxidized LDL is itself toxic to endothelial cells, compounding the endothelial injury. It is also chemotactic to monocytes and immobilizes macrophages, favoring their accumulation at sites of atheroma formation.

Further, it is also taken up by macrophages and smooth muscle, cells much more avidly than native LDL, by pathways different from those used by native LDL. Hepatocytes and other cells have specific receptors for native LDL, accounting for the removal of about two thirds of plasma LDL. Oxidized LDL, however, is taken up through a "scavenger pathway" that does not involve the usual LDL receptors but rather high affinity receptors, specific for modified LDL. Other modifications of LDL may also facilitate its uptake. LDL within arterial walls may complex with certain proteoglycans to form insoluble complexes that are avidly taken up by macrophages. Still other complexes may be formed, all of which are taken up more rapidly than native LDL. Thus much of the lipid content of atheromas is thought to be oxidized LDL, and indeed it has been shown that it is possible to confer some protection against atherosclerosis in rabbits by treating them with antioxidants. Another variant of LDL (a complex of LDL linked to apo a by disulfide oxides) called lipoprotein **a** (LP**a**) has also been identuified. Elevated levels are genetically determined, and low-fat diets, lipid-lowering drugs, other interventions have no effect on the blood levels. LP**a**'s precise role in atherogenesis is now under study.

C. A complex series of cellular events are involved in the formation of atheromartous plaques. Following adhesion to endothelial cells, monocytes migrate between endothelial cells to localize subendothelially. There they become transformed into macrophages and avidly engulf lipoproteins, largely oxidized LDL, to become **foam** cells. Oxidized LDL is chemotactic to monocytes and immobilizes macrophages at sites where it accumulates. In addition, early in the evolution of the lesion, smooth muscle cells cells (SMC-s), some of medial origin, gather in the intima, where they and some take up lipids to also be transformed into foam cells. As long as the hypercholesterolemia persists, monocyte and lymphocyte adhesion, subendothelial migration of SMC-s, and accumulation of lipids within the macrophages and SMC-s continue to eventually yield aggregates of foam cells in the intima, which are apparent macroscopically as **fatty-streaks**. These, many believe, are the forerunners of fully evolved atheromas. Should the hypercholesterolemia be ameliorated, these fatty streaks may regress, but if they persist they continue to evolve.

D. **Proliferation of SMCs** about the focus of foam cells converts the fatty streak into a mature fibrofatty atheroma. It has been clearly shown that arterial SMCs can synthesize collagen, elastin, and glycoproteins. A number of growth factors have been implicated in the proliferation of SMCs, most importantly **platelet-derived growth factor (PDGF)**, released from platelets adherent to the focus of endothelial injury but also produced by macrophages, endothelial cells, and SMCs in response to the release of cytokines (e.g., tumor necrosis factor [TNF], interleukin-1 [IL1] and

interferon [IFN] – gamma) generated by macrophage-lymphocyte interactions. Additional candidate mitogens are fibroblast growth factor, epidermal growth factor, and transforming growth factor alpha (TGF-alpha). Indeed, the evolving atheroma has been likened to a chronic inflammatory reaction, with activated T-cells, monocyte/macrophages, endothelial cells and SMCs all expressing or contributing a variety of cytokines, which could play role in cell adhesion, locomotion and replication. Theoretically, SMC proliferation might also result from loss of growth inhibitors such as heparin-like molecules present in endothelial and smooth muscle or TGF-beta derived from endothelial cells or macrophages.

At this stage in atherogenesis, the intimal plaque represents a central aggregation of foam cells of macrophage and SMC origin, some of which may have died and released extracellular lipid and cellular debris surrounded by SMCs, and possibly fibroblasts of arterial wall origin embedded within a scant connective matrix.

With progresion, the cellular-fatty atheroma is modified by the further deposition of collagen, elastin, and proteoglycans. This connective tissue is particularly prominent on the intimal aspect, where it produces the so-called **fibrous** cap. Thus evolves the fully mature **fibrofatty atheroma.** Some atheromas undergo considerable cellular proliferation and connective tissue formation to yield **fibrous plaques.** Others retain a central core of lipid-laden cells and fatty debris. Whether cellular atheromas represent the end stage of fibrofatty lesions is not clear.

Two other theories of atherogenesis merit brief mention. These theories, including the response-to-injury proposal, are not mutally exclusive, and conceivably all proposed mechanisms may collaborate in atherogenesis.

II. **The monoclonal hypothesis** proposes that so-called fibrous plaques are monoclonal or at least oligoclonal (i.e. are composed of the progeny of a single SMC or a few cells) stimulated to proliferate by mutagens, possibly viruses, or fractions derived from cholesterol or tobacco smoke. Thus, in effect the cellular plaque is likened to a smooth muscle tumor. In theory such cellular lesions might then accumulate lipoproteins in hypercholesterolemic persons. Subsequent studies have disproven the monoclonality of cellular plaques and have contended that their oligoclonal makeup simplu reflects the overgrowth of more vigorous cells in the area of arterial wall injury.

III. Yet another hypothesis may be termed the **thrombogenic or encrustation theory** (i.e., plaques arise from mural thrombi over foci of endothelial injury). Organization and reendotelization of the thrombi, in effect, incorporate them into the intimal layer, and it is the breakdown of the blood constituents that yields the lipid content. While thrombi may well for over preexisting ulcerated atheromas and be

incorporated into the evolving lesion and may also worsen the luminal narrowing, it is doubtful that they constitute the origins of atheromatous lesions.

Each of the several pathogenic sequences cited has theoretically attractive features that could participate in atherogenesis, so it may well be that "more than one road leads to Rome".

II.2.2. Pathophysiology of ischemic heart disease (coronary artery disease)

Ischemic heart disease, also called coronary heart disease, is the generic designation for a group of closely related syndromes that result from an imbalance between the cardiac need for oxygenated blood and its supply. Coronary blood flow provides oxygen and metabolic substrates to the heart. In addition, coronary flow allows for the efficient removal of metabolic end products such as lactic acid, hydrogen ions and carbon dioxyde. Thus, a reduction in coronary blood flow not only reduces myocardial oxygen supply but also reduces the ability to remove the end-products of myocardial metabolism.

A critical balance exists between myocardial oxygen supply and demand: oxygen supply must equal demand. A reduction in oxygen supply or an increase in oxygen demand can disturb this balance and threaten myocardial function.

Ischaemia is a transient, reversible state of oxygen lack. Prolonged ischaemia will lead to muscle death and **necrosis.** Clinically, necrosis of the myocardium is reffered to as myocardial infarction.

Ischaemia is the consequence of the inbalance between myocardial oxygen supply and myocardial oxygen demand.

1. Determinants of myocardial oxygen demand.

There are four major determinants of myocardial demand:

a. the heart size
b the left ventricular systolic pressure
c. the heart rate
d. the level of myocardial inotropic state

Therefore, cardiac work and oxygen demand are elevated by:

- tachycardia (rapid heart rates)
- increased force of contraction (thyrotoxicosis, drugs)
- hypertension
- ventricular dilation and ventricular hypertrophy

II. Determinants of myocardial oxygen supply

The amount of oxygen used by the heart is directly related to:

a. the coronary blood flow

b. the oxygen of arterial blood

c. the amount of oxygen extracted from the blood by the heart

To significantly increase oxygen supply, coronary flow must increase because myocardial oxygen extraction from the arterial blood is almost maximal under resting conditions.

According these conditions, the decrease in oxygen supply may be the consequence of:

1. reduced coronary blood flow

- coronary flow obstructionn
- atherosclerotic plaque
- thrombus formation
- emboli
- trauma or congenital abnormalities of coronary arteries
- arteritis (lupus eritematous)
- amiloidosis

b. hemodynamic causes:

- fall in dyastolic pressure below the autoregulation range
- hypotension, aortic insufficiency
- inadequate dyastolic perfusion time (rapid heart rates)

c. functional causes:

- coronary artery spasm
- increased blood viscosity (thrombocytosis, polycitemia vera, hypercoagulability)

2. reduced oxygen content of coronary artery:

- severe anemia
- carbon monoxyde poisonning

PATHOPHYSIOLOGY

1. Mechanisms of unbalance between myocardial oxygen supply and myocardial oxygen demand

If myocardial oxygen demand increases, oxygen supply must increase concurrently. The augmentation of coronary flow is the only practical mechanism by

which increased metabolic demands can be met. The most potent stimulus to dilating the coronary arteries and increasing coronary flow is local tissue hypoxia. The normal coronary vasculature can dilate and increase flow approximately 5 to 6 times above resting levels. However, because stenotic, diseased vessels are unable to dilate, a state of oxygen deficit can result when oxygen demand exceeds the capacity of the vasculature to increase flow.

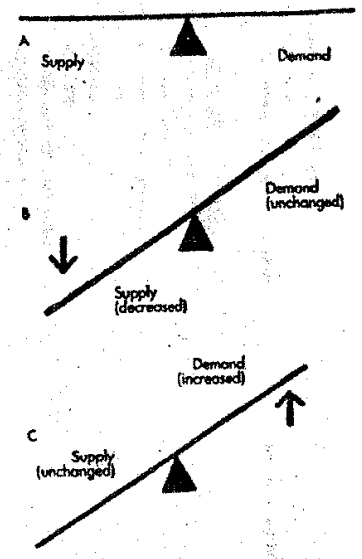


Figure no. 19 Balance between myocardial oxygen supply and demand. A, Normally, myocardial oxygen supply and demand are in balance. B, Imbalance caused by decreased coronary blood supply (such as low blood pressure) while the demand for oxygen remains unchanged. C, Imbalance caused by increased demand (such as exercise) while the blood supply to the myocardium remains unchanged (coronary atherosclerosis limits ability of the blood vessels to increase supply). (Adapted from Clark MC: Chest pain. Heart Lung 4:956, 1975.)

The left ventricle is the chamber most susceptible to myocardial ischaemia and infarction because of its unique myocardial oxygenation characteristics. First, left ventricular oxygen demand is great as a result of the high systemic resistance to ejection and the large muscle mass. In addition, coronary flow is phasic in nature. The branches of the coronary arteries are deeply embedded in the myocardium. During sygtole, these intramyocardial branches are compressed, which increases the resistance to flow. Coronary flow, therefore, occurs primarily during dyastole. Contraction of the thick left ventricular wall essentially terminates systolic flow through its intramyocardial branches, especially in the inner most of subendocardial region, some systolic flow continues in the vessels of the thinner wall right ventricle.

II. Consequences of the ischaemia

Transient ischaemia causes reversible changes at the cellular and tissue levels, depressing myocardial function. The oxygen lack forces the myocardium to shift from aerobic metabolism to anaerobic metabolism. Anaerobic metabolism via glycolytic pathways is a much less efficient means of energy production than is aerobic metabolism via oxydative phosphorilation and the Krebbs cycle; the production of high energy phosphate is reduced considerably. The end product of anaerobic metabolism, lactic acid, accumulates, reducing cellular pH.

The combination of hypoxia, reduced energy availability and acidosis rapidily impairs left ventricular function. The strength of contraction in the affected myocardial region is reduced, the fibers shorten inadequately with less force and velocity. In addition, the wall motion of the ischaemic segment is abnormal, the segment passively bulges outward with each ventricular contraction.

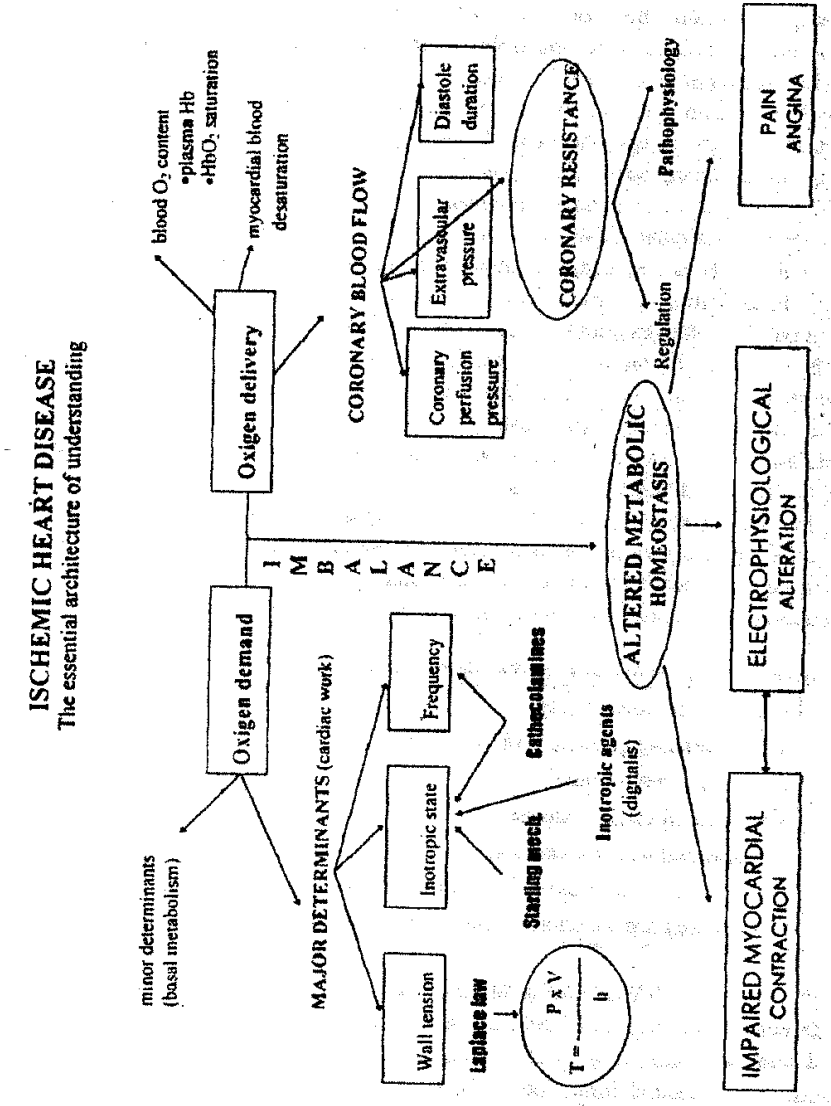
The reduced contractility and impaired wall motion alter hemodinamics. The hemodinamic response is variable, depending on the size of the ischaemic segment and the degree of reflex compensatory reponse by the anatomic nervous system. Depression of the left ventricular function may lower cardiac output by reducing stroke volume. Reduction in systolic emptying increases ventricular volumes. As a result, left sides pressures, the left ventricular end-dyastolic pressure and pulmonary capillary wedge pressure rise. This pressure elevation is magnified by changes in wall compliance or distensibility induced by ischaemia. A reduction in compliance occurs, accentuating the elevation in pressure for a given ventricular volume.

Table 14 - Left ventricular dysfunction related to ischaemia

• decreased contractility
• abnormal ventricular wall compliance
• abnomal wall motion
• decreased stroke volume
• decreased ejection fraction
• increased ventricular end-systolic and dyastolic volumes
• increased left ventricular end-dyastolic pressure

FORMS OF CORONARY ARTERY DISEASE

Depending on the rate of development of the ischemia and its ultimate severity, one of four syndromes may result: 1. angina pectoris (AP), of which there are three variants, 2. myocardial infarction (MI), the predominant form of IHD; 3. chronic ischemic heart disease, (CIHD, ischemic cardiomiopathy); and 4. sudden cardiac death, (SCD), which may be superimposed on any of the other three conditions. Before any of these overt disorders becomes manifest, there is a decades-long prodrome of silent, slowly progressive coronary atherosclerosis.



ANGINA PECTORIS

Angina pectoris means anxiety (pain) on the chest. It is a syndrom provoked by a transitional myocardial ischemia. Chest pain is of short duration and is typically localized retrosternally.

Angina subtypes:

- stable
- unstable
- variant

Stable angina

Is a basically syndrom caused by a transitional myocardial ischemia.

Characteristics of chest pain

1. Quality
   - Pressure of heavy weight on the chest
   - Burning
   - Tightness
   - Constriction about the threat
2. Location
   - over sternum or very near to it anywhere between epigastrum and pharynx
   - occasionally limited to the left shoulder and left arm
3. Radiation
   - medial aspect of the left arm
   - left shoulder
   - jaw
4. Duration - 5 to 30 minutes
5. Precipitating factors
   - relationship to exercise
   - cold environment
   - walking against the wind
   - walking after a large meal
   - emotional factors
6. Nitroglycerin relief - relief of pain occuring within 45 seconds to 5 minutes of taking nitroglycerin
7. Associated symptoms
   - shortness of breath
   - dizziness, syncope
   - palpitations
8. Electrocardiographic changes - T wave inversion and ST segment depression

Pathophysiology

In most instances, classic AP produced by exertion and relieved by rest, is the result of atherosclerotic obstruction of the coronary arterial tree. Several anatomical sites of obstruction are possible; the major coronary arterial trunks and their epicardial bunches, the coronary ostia at the aorta and the small vessels that are located intramyocardially. Coronary narrowing can also result from various diseases (arteritis, cardiomyopathy, amiloidosis).

The coronary reserve, or the ability to increase coronary blood flow by vasodilation, is reduced when a stenotic lesion reduces the coronary lumen by as little as 30%. When the coronary lumen is reduced by 90%, coronary reserve is minimal. With this degree of stenosis, coronary blood flow is adequate at rest but cannot incease in response to acute increases in metabolic demands. Coronory reserve becomes limited in the subendocardium before the subepicardium. Ischaemic attack normally subsides within minutes if the inbalance between oxygen supply and demand is corrected. The metabolic, functional, hemodynamic and electrocardiographic changes are reversible.

UNSTABLE ANGINA

Based on clinical criteria, there are two relatively distinct types of patients within the group called unstable angina. One type includes patients **without previous angina** who suddenly begin to experience repeated episodes of chest pain, often at rest, frequently at night or in the early morning or with a very low level of effort.

The other type of patient has a **long history of effort angina** which either increases in frequency, occurs with less effort or progresses to rest angina. The assumption underlying these descriptions is that the patient has very severe, extensive, rapidly progressive coronary atherosclerosis.

Table 15 - Coronary vascular factors involved in unstable angina

Condition	Multivessel disease
Coronary atherosclerosis	Plaque rupture / disruption
	Coronary spasm (obstructive)
Dynamic coronary artery changes	Increased tone (non-obstructive)
	Microvascular spasm
	Increased arteriolar tone
Intimal injury	Platelet deposition and non-oclusive thrombus
	Leucocytes (monocytes and macrophages)
Causes	Thromboxane and leukotriens

Pathophysiology

The following mechanisms are involved:

I. Complicated coronary atherosclerosis

II. Dynamic coronary artery changes

III. Intimal injury

I. Coronary atherosclerosis

The coronary arteries of most patients with chronic stable effort angina show severe multivessel atherosclerosis as a rule. Although the clinical manifestations and pathophysiology of unstable angina differ from those associated with stable effort angina, the extent and distribution of coronary atherosclerotic obstructions are in general not different. The number of diseased vessels and degree of obstruction are remarcably similar. What is responsible for the change in symptoms or onset of symptoms to include ischaemia at rest?

Studies suggest that morphology of the coronary lesion may be different in unstable angina. Pathologic examination of coronary artery lesion showed that the appearance of these lesions was due to plaque rupture or partially ochusive thrombi. The lesions were described as "complicated lesions". Study of these lesions indicates that thrombus develops at sites of plaque disruption that relate to tears in its overlying fibrous cap.

II. Dynamic coronary artery changes

It is generally agreed that intense arterial spasm reduces blood flow, resulting in ischaemia or infarction in the distribution of the artery. Localized, large coronary artery vasomotor changes that do not completely occlude the vessel could affect the coronary artery in other ways. Vasomotor changes may account for morphologic changes (plaque rupture and non-occlusive thrombi). Also, focal arterial constriction, which does not reduce flow, may damage the arterial wall itself

Alterations in Tx A2 production may also produce a local inbalance between PgI2 and TxA2, resulting in platelet adhesion and aggregation. Platelets from the patients with atherosclerosis produce increased amounts of TxA2 suggesting a predisposition to platelet aggregation.

Role of leucocytes

Leukocytes accumulate progressively during the initial hours of acute myocardial ischaemia. Leukocytes plug capillaries in regions with low blood flow, thus increase coronary vascular resistance. During reperfusion leukocyte accumulation increases and the adherent leukocyte plug cannot be dislodged, preventing restoration of capillary flow (the no-reflow phenomenon).

a. Leukocyte accumulation

Several mechanisms contribute to leukocyte accumulation and activation during acute myocardial ischaemia. Leukocytes are large, stiff and are adherent to the vascular endhotelium. The decrease in perfusion pressure during acute myocardial ischaemia increases leukocyte adhesion and leads to accumulation. Several mechanisms contribute to chemotaxis during acute myocardial ischaemia. Platelets release platelet activating factor (PAF) and 12-hydroperoxyeicosotetranoic acid (12 HPETE) which are chemotactic. The complement system is activating during acute myocardial ischaemia with resultant chemotaxis.

Several products of arachidonic acid, including those from activated platelets and neutrophils, contribute to chemotaxis. The major leukotrien product of neutrophils is LTB4, which is a potent chemotactic agent. Neutrophils from patients with stable angina pectoris have increased activity and increased potential for LTB4 production. Patients with unstable angina and acute myocardial infarction have evidence of intense activation of neutrophils.

b. Leutocyte-mediated damage.

Neutrophils accumulated at the site of acute myocardial ischaemia may produce myocardial damage by producing, oxydants and / or releasing a large number of proteolytic enzymes.

Oxygen-derived free radicals, particularly the hydroxyl radical, produce extensive structural alterations in the vascular endothelium and mytochondria. Damage to the vascular endothelium is manifest by increased vascular permeability and increased coronary artery perfusion pressure. In addition to direct damage, the superoxyde anion can inactivate EDRF from the vascular endothelium.

Table 16 - Aggravating factors in unstable angina

Factor	**Examples**
Environement	Smoking
	Stress (emotional stress)
Associated illness	Cold exposure
	Anemia
	Thyrotoxicosis
	Hypertension
	Arrthytmia
	Infection
	Polycytemia
	Hypoxemia
	Antihistamine preparations
Vasoconstricting drugs	Illegal drugs (e.g. cocaine, amphetamine)

The membrane of neutrophils contains the enzyme NADPH oxydase, which is activated to shutle electrons from cytosolic NADPH to dissolved oxygen in the

extracellular fluid to produce superoxyde anion ($0_2^{\bullet}$), hydroxyl radical ($OH^{\bullet}$, and hydrogen peroxyde (H_20_2). Oxygen derived free radicals are directly cytotoxic and induce additional damage by reacting with non-radicals to nitrate a chain reaction of free radical production.

Oxygen-derived free radicals or the products of the chain-reaction of free radical production, cause extensive damage by peroxydation of membrane phospholipids and inactivation of important enzymes.

VARIANT ANGINA

The term Prinzmetal's variant angina" applies to a relatively specific subset of patients with unstable angina which includes only patients with ST segment elevation accompaning rest pain.

Pathophysyology

In contrast to exertion-induced angina pectoris, in which the pain and myocardial ischaemia reflect an inadequate increase in coronary blood flow through the diseased coronary vessels as myocardial work and oxygen demands increase, variant angina occurs due to a transient reduction in coronary flow. There is little doubt that **focal spasm** is responsible for the reduction in coronary flow and causes transient transmural myocardial ischaemia, resulting in the chest pain. The coronary spasm tends to be focal and frequently occurs at an area of atherosclerotic plaque or abnormality in the vessel.

The fact that the spasm tends to occur in areas of abnormality or atherosclerotic plaques suggests a local hyperactivity in the wall of the coronary artery.

Many hypothesizes have been proposed for the precipitating causes of this focal spasm, including increased vagal tone during sleep. Other hypotehsis have centered around the general or local release of vasoconstrictive substances such as TxA2 or sympathomimetic amines.

SILENT ISCHAEMIA

By definition, silent ischaemia occurs when there is objective evidences of ischaemia in the absence of symptoms.

The silent ischaemia is the most common form of ischaemia and yet often remains untreated because it is unrecognized.

Mechanisms for the absence of discomfort in silent ischaemia Three major mechanisms have been proposed as to why silent ischaemia does not manifest itself as a clinical symptom in some patients with coronary artery disease 1. Impaired neural pathways 2. Insufficient ischaemia to produce discomfort 3. Altered pain threshold

1. The peripheral neuropathy of diabetes may contribute to silent ischaemia in some patients. Also, acute myocardial infarction itself may damage neural pathways and thus interfere with the appreciation of ischaemia from a closely related zone of myocardium.

Table 17 - Technique for diagnosing silent ischaemia

Electrocardiogram
• Standardized treadmill test
• Ambulatory EKG (flat or down sloping ST depression of at least 1 mm with a gradual onset and offset of the episodes, all of which last at least one minute)
Coronary blood flow
• Thallium 201
• Rubidium 82
Hemodynamics
• Regional wall motion
• Rise in pulmonary capillary wedge pressure
Metabolism
• Lactate production

2. Insufficient ischaemia to reach the pain threshold is also a possible explanation in some patients. Event through electrocardiographic or regional wall motion changes occur, the patient may be unaware of it.
3. A third factor that may be involved is a differing pain threshold in different patients. Asymptomatic patients with myocardial ischaemia tend to have higher pain threshold than those with symptomatic myocardial ischaemia.

II.2.3. Pathophysiology of acute myocardial infarction

Prolonged ischaemia of over 30 to 45 minutes causes irreversible cellular damage and muscle death or necrosis. Permanent cessation of contractile function occurs in the necrotic or infarcted area of the myocardium. The infarct is surrounded by a zone of ischaemia, potentially viable tissue. The ultimate size of the infarct depends on the fate of this ischaemic zone, Necrosis of this marginal area extend the infarct size, whereas reversal of the ischaemia minimizes the residual necrosis.

Myocardial infarction usually affects the left ventricle. A **transmural infarction** involves the full thickness of the wall, a **subendocardial infarction** is limited to the inner half of the myocardium.

I. Causes of acute myocardial infarction

The causes of acute myocardial infarction can be those that limit myocardial oxygen supply and / or those that increase myocardial oxygen demand.

An atherosclerotic plaque in the coronary artery is by far the most common cause for reduced coronary blood flow.

1. The atherosclerotic plaque in acute myocardial infarction

Alteration in the integrity of the plaque appears to be important in the pathophysiology of myocardial infarction.

Dysruption of the atherosclerotic plaque is frequently observed on postmortem examination of patients who have died of AMI.

A dysrupted plaque may serve as the nidus for thrombus formation. The thrombus frequently contains platelet aggregates or substances from the atherosclerotic plaque, such as cholesterol crystals, foam cells and intimal collagen fibers. These findings support the concept that plaque rupture precedes (or leads to) thrombus formation.

The precise mechanisms for initiating plaque dysruption are not known. It has been postulated that plaque dysruption occurs as a consequence of chronic hemodynamic trauma, inflammatory or chemical injury to the endothlelium, or coronary artery spasm. The normal twisting and banding motion of the heart and its arteries is another possible mechanism for tearing the thin fibrous cap of the atherosderotic plaque.

Dysruption of the atherosclerotic plaque could lead to acute coronary artery occlusion and myocardial ischaemia by several mechanisms. Injury to the endothelial barrier produces a communication between the coronary lumen and the atherosclerotic plaque, which allows blood, fibrin and platelet to infiltrate into the plaque, resulting in further obstruction of the coronary lumen. Intraintimal thrombus formation also increases intraplaque pressure, leading to further plaque rupture. Another mechanism for initiating coronay artery occlusion occurs when the contents of the ruptured plaque is released into the coronary lumen and embolizes into the distal coronary bed. The perfusion bed distal to the site of an acute thrombus often contains platelet and fibrin microemboli and microinfarcts.

Another possible mechanism for occluding blood flow involves intraluminal thrombus. A rupture or break into the fibrous cap of the atherosclerotic plaque exposes the necrotic core and collagen fibers of the plaque to the overlying coronary blood flow. This serves as a nidus for thrombus more frequently when the underlying plaque already produces significant coronary artery stenosis. Such plaque may be subjected to greater mechanical trauma because of the increased local turbulence associated with severe coronary artery stenosis.

2. Coronary artery thrombosis

Contact of circulating platelets with exposed subendothelial collagen fibers and microfibrils initiates platelet adhesion and aggregation. The incidence of coronary thrombi in patients with acute myocardial infarction is greater than 80% in the majority of several large autopsy series. Thrombus is most often found at the site of

an atherosclerotic plague, particularly if the plaque occludes 75% or more of the coronary lumen and / or if there is a long area of stenosis.

Intracoronary thrombi occur more frequently with transmural and larger infarcts. In contrast, the incidence of coronary artery thrombosis is lower in patients with subendocardial myocardial

3. Coronary artery spasm

AMI can occur as a consequence of coronary artery spasm. Coronary artery spasm can be demonstrated in many patients with unstable or crescento angina. These same vessels can subsequently occlude and produce AMI. Coronary artery spasm may be an important precursor of AMI in patients with variant angina. The mechanisms for coronary artery spasm include:

- local inbalance between TxA2 and PgI2 production
- humoral factors (histamin and serotonin)
- increased alpha-adrenergic stimulation, which leads to abnormal autoregulation of coronary arteries.
- endothelial dysfunction (reduced EDRF production by atherosclerotic vessels)

II. Metabolic consequences of AMI

Within 30 to 60 seconds of abrupt coronary artery occlusion, myocardial oxygen tension in the ischaemic zone falls to near zero levels. There is a rapid shift from aerobic to anaerobic cardiac metabolism.

The cardiac stores of high energy phoshates are limited and are rapidly depleted. The only other significant source of high energy phosphates is derived from anaerobic glycolysis. Lactic acid is produced during, anaerobic metabolism. Lactic acid accumulates since it neither can be metabolized further nor removed adequately because of the decrease in coronary blood flow. The accumulation of lactic acid, hydrogen ions and NADH inhibits glycolysis, thus limiting the only significant source of ATP generation under anaerobic conditions.

The anacrobic generation of high energy phosphates is not sufficient to meet the energy demands of the ischaemic myocardium, even the myocardial oxygen demands being reduced because of the decrease in myocardial contractility

Myocardial contractile function declines as ATP stores are depleted and tissue acidosis develops. However, the early ischaemic dysfunction develops before high energy phosphate stores are depleted. The early ischaemic dysfunction may be related to:

- decreased ATP in specific cellular compartments
- increased inorganic phosphate (from hydrolysis of creatin phosphate and ATP) which cause a marked decrease in myofilament sensitivity to calcium

- local tissue acidosis, by decreasing myofilament sensitivity to calcium
- decrease in calcium availability and/or decreased myofilament sensitivity to calcium

If ischaemia is prolonged, cardiac myocytes undergo irrversible damage even if coronary perfusion is restored. This irreversible stage of injury is characterized by ultrastructural alterations, including marked glycogen depletion, diffuse mithocondrial sweelling, accumulation of amorphous densities in the matrix of the mithocondria, peripheral aggreagation of nuclear cromatin and small breaks in the plasmalemma of the sarcolemma.

Several products that are produced during myocardial ischaemia can contribute to myocardial dysfunction and permanent damage. If acid lactic accumulates during myocardial ischaemia recovery of ventricular function following reperfusion requires a longer time and is less complete then when lactic acid does not accumulate. Circulating catecholamines levels increase in patients with AMI. Increased catecholamines produce arrythmias, increase myocardial oxygen consunption and cause oxygen wasting due to mithocondrial uncoupling.

Catecholamines also activate triglyceride-lipase in adipose tissue and suppress insulin secretion. As a result, circulating free fatly acid level increase during AMI.

Catecholamines also promovate intramyocardial lipolysis. Nonesterified fatty acids accumulate in the ischaemic region, particularly in the subendocardium and exert the following effects:

- negative inotropic effect on the heart
- depletion of intracellular glycogen
- alterations in membrane permeability (leading to cell damage)
- inhibition of calcium transport in the sarcoplasmic reticulum.

These alterations contribute to the functional impairement and arrythimia during acute myocardial ischaemia.

Finally, oxygen derived free radicals produced during acute myocardial ischaemia may contribute to myocardial damage, particularly with reperfusion.

Functionally, myocardial infarction results in changes similar to those noted with ischaemia.

III. Diagnosis of AMI

Myocardial infarction is classically associated with a characteristic diagnostic triad.

First, the typical clinical picture consists of severe prolonged chest pain frequently associated with sweating, nausea, vomiting and a sense of impending doom.

Second, serum levels of the cardiac enzymes released by the necrotic myocardial cell are elevated. The released enzymes include creatine phosphokinase (CPK), aspartate aminotrangferase (ASAT) and lactic dehydrogenase (LDH).

Creatin kinase levels rise rapidly, peaking at 24 h, with slower rises being shown by ASAT and LDH. Measurement of izoenzymes increases diagnostic accuracy. Release of the MB-CPK izoenzyme is the most specific enzymatic indication of myocardial infarction.

Finally, electrocardiographic changes, consisting of pronounced Q waves, ST segment elevation and inverted T waves, are evident during AMI.

In 30% of patients diagnosed with an infarct no Q waves develop, this aspect suggesting subendocardial infarction.

IV. Consequences of AMI

A wide spectrum of left ventricular dysfunction is apparent after myocardial infarction. The degree of functional impairment depends on a number of factors.

1. **Infarct size** infarcts over 40% of myocardium are associated with high incidence of cardiogenic shock.

2. **Infarct location:** anterior wall infarction is more likely to significantly depress mechanical function than is inferior wall damage.

3. **Function of uninvolved myocardium:** old infarcts would compromise residual myocardial function.

4. **Collateral circulation:** collateral circulation via either preexisting arterial anastomosis or new channels can develop in response to chronic ischaemia and regional hypoperfusion improving blood flow to threatened myocardium.

5. **Cardiovascular compensatory mechanisms**

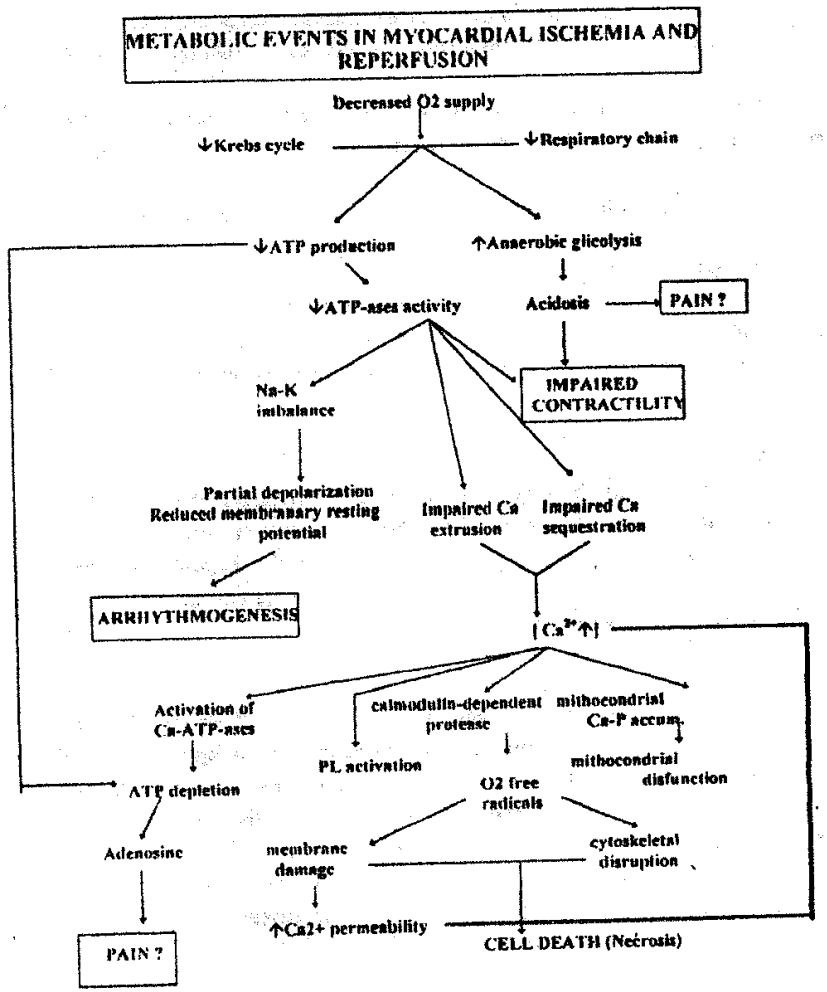
Reflex compensatory mechanisms operate to maintain cardiac output and peripheral perfusion.

A battery of reflex responses are available to forestall deterioration of cardiac output and perfusion pressure:

- augmentation of heart rate and contractility
- generalized vasoconstriction sodium and water retention
- ventricular dilation
- ventricular hypertrophy

Reflex sympathetic augmentation of the heart rate and contractility can impair ventricular function. Generalized arteriolar constriction increases total peripheral resistance, thereby increasing mean arterial pressure. Venoconstriction reduces venous capacity, increasing venous return to the heart and ventricular filling. Increased ventricular filling elevates the force of contraction and subsequent ejection volumes. With depression of ventricular function higher dyastolic filling pressure are

necessary to maintain stroke volume. Elevation of dyastolic filling pressure and ventricular volume stretches myocardial fibers, increasing the force of contraction according to Starling's law. Circulatory filling pressure can be increased further by renal retention of sodium and water. As a result, myocardial infarction is commonly associated with transient left ventricular enlargement caused by compensatory cardiac



dilation. If necessary, compensatory cardiac hypertrophy can also occur to increase force of contraction and ventricular emptying.

Complications of AMP

Electrical disturbaces

1. **Dysrhytmias** arise in virtually all patients suffering from AMI, amounting for about half of the deaths from coronary heart disease. Sinus bradycardia, premature ventricular beats, ventricular tachycardia, ventricular fibrilation, paroxysmal atrial tachycardia can occur.

2. **Conduction abnormalities** include A-V nodal blocks of the first degree, second degree, third degree and intraventricular blocks such as hemiblocks and bundle's branch blocks.

3. **Electromechanical dissociation** can also outset in these patients.

Pump dysfunction

1. **Contractile dysfunction:** left ventricular, right ventricular and biventricular failure, true ventricular aneurism, infarct expasion.

2. **Cardiogenic shock** occurs when the infarct involves more than 40% of the left ventricle mass.

Rupture

It may occur within the first 21 days. Extremal rupture of the ventricle produces pericardial tamponade. It occurs frequently in women and in patients with hypertension; false aneurysm can result from if ruptured ventricle is walled off. The interventricular septum rupture may occur. Acute mitral regurgitation can result from papillary muscle dysfunction or rupture.

Aneurysm

Following acute transmural AMI the ventricluar wall bulges outward dusing systole in 1/3 of patients As the infarct maturates the collagenous scar tissue is susceptible to stretching. Occurence of myocardial thinning and stretching in this region is termed "infarct expansion", being actually an early aneurysm; intraneurysmal thrombi are a source of systemic emboli.

A "true" aneurysms are caused by bulging of the weakened but intact left ventricular wall. A "false" aneurysms result from the rupture of a portion of the left ventricle that has been walled off by pericardial scar tissue.

Ischaemia

1. Postinfarction ischaemia
2. Early recurrent infarction or infarct extension

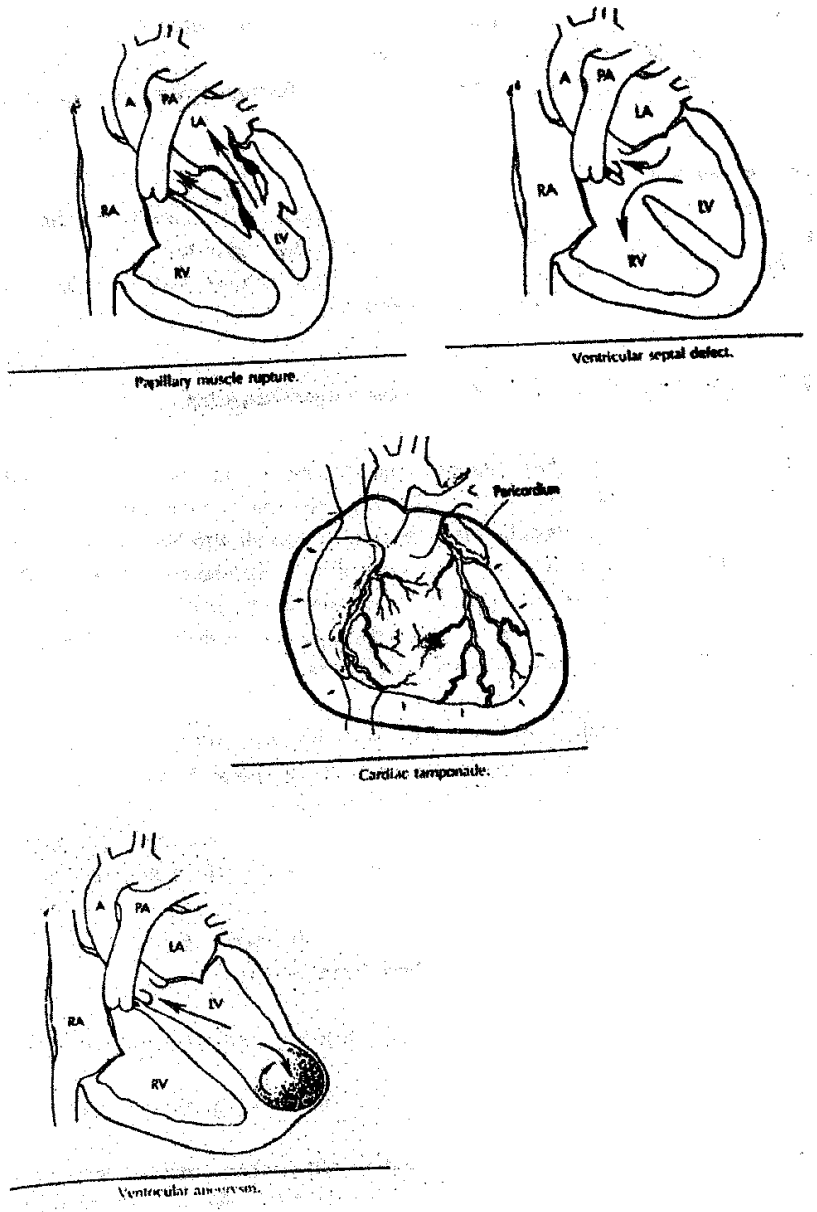


Figure no. 20. Complications of myocardial infarction

Pericarditis

1. Early (epistenopericarditis) usually occurs on the area of the heart surface that overlies the necrotic muscle in transmural infarcts.

2. Late (Dressler's syndrome, postmyocardial infarction syndrome) arises as early as 2 weeks and as late as 2 years after AMI.

Thromboembolic

1. Mural thrombosis with systemic embolism results from endocardial damage during AMI and subsequent adhesion of platelets and fibrin deposition.

2. Peripheral embolization and infarcts of various organs such as deep vein thrombosis with pulmonary embolism are possible.

II.2.4. Pathophysiology of arterial hypertension

Definition

Hypertension (HT) is an abnormal elevation of systolic and / or dyastolic blood pressure (BP), either primary or secondary. HT is defined somewhat arbitrarily. Most, would agree that a sustained dyastolic pressure greater than 90 mm Hg is an essential feature. A sustained systolic pressure in excess of 140 mm Hg also constitutes HT.By means of these criteria, the percentage of HT persons in the general population in screening programs is 25%. However, most surveys use systolic and dyastolic pressure of 165/95 mm Hg as the dividing line for adults.

Hypertension:

- is a major health problem in most societies; it is very common.
- numerous studies have documented that the higher the BP, the greater the risk for a variety of cardiovascular events, including stroke, cerebrovascular accidents and myocardial infarction and may lead to congestive heart failure and to renal failure; its effects are sometimes devastating.
- HT remains asymptomatic until late in its course. Elevated BP is a staggering health problem for these three reasons.

Prevalence

The prevalence increases with age, although when present in young adults it tends to be more severe.

Blacks are affected about twice as often as whites and apparently are more vulnerable to its complications.

Although females are hypertensive more often than males, this sex preponderence is limited to the alder age groups, in which the disease is likely to be relatively benign. Before 50 years HT is more common in males.

Blood pressure regulation

There are two fundamental hemodynamic variables that determine the magnitude of arterial pressure (fig. 21).

They are:

- cardiac output (CO) = total systemic blood flow
- total peripheral resistance (TPR) = resistance offered by the blood vessels to forward flow.

Arterial pressure is a product of CO and peripheral resistance. These two are in turn affected by a variety of factors; these factors are shown as affecting either vascular resistance or CO (fig.21).

HT can result from any factor which alters the relationship between CO and TRP.

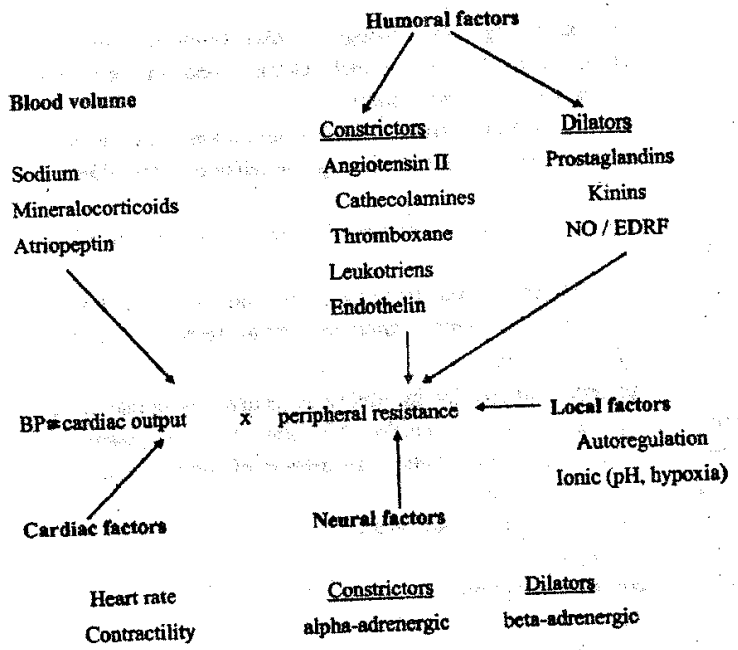


Figure no. 21
Blood pressure regulation.

In reality, most of these factors act at several points: for example, angiotensin not only causes vasoconstriction but also stimulates aldosterone secretion, which in turn affects water retention and fluid volume. Analogously, salt retention not only

increases cardiac output but may also increase peripheral resistance by altering the sensitivity of the vascular smooth muscle to vasoactive stimuli. Such interactions are too numerous to detail, but several examples have been cited to emphasize that in most hypertensive persons elevation of blood pressure results from an interaction of multiple factors.

The vascular system responds quickly to changes in the effective rates of flow through tissue beds by autoregulation .

In the case of HT, the end result of autoregulation is always incresed peripheral resistance.

The kidneys

They play an important role in blood pressure regulation by:

1. The renin-angiotensin system.
2. Sodium homeostasis.
3. Renal vasodepressor substances.

1. The renin-angiotensin system (fig. 22). Through the elaboration of renin the kidney eventually forms angiotensin II (AII), which alters blood pressure by increasing both peripheral resistance and blood volume.

RENIN secretion is controled by 4 mechanisms that are not mutually exclusive:

1) Renal vascular receptor that responds to changes in tension in the afferent arteriolar wall.
2) Macula densa receptor that detect changes of concentration of NaCl in distal tubule.
3) A negative feed back effect of circulating angiotensin on renin secretion.
4) Sympathetic nervous system, which stimulates renin secretion via the nerve mediated by β receptors.

The former effect is achieved largely by its ability to cause vasoconstriction through direct action on vascular smooth muscle, the latter by stimulation of aldosterone secretion, which increases distal tubular reabsorbtion of sodium, and thus of water, so enhancing total body fluid volume.

The R-Ag system elevates BP by three mechanisms:

a. Increased sympathetic output
b. Increased mineralo-corticoid secretion
c. Direct vasoconstriction.

This axis is antagonized by a hormone, atrial natriuretic factor, secreted by specialized cells in the atria.

This factor, acting via its own receptors, increases the urinary excretion of sodium that opposes the vasoconstrictor effect of Ag II. Secretion of atrial natriuretic factor may be controlled by atrial distension, a consequence of increased volume, or by as yet undefined endocrine interactions.

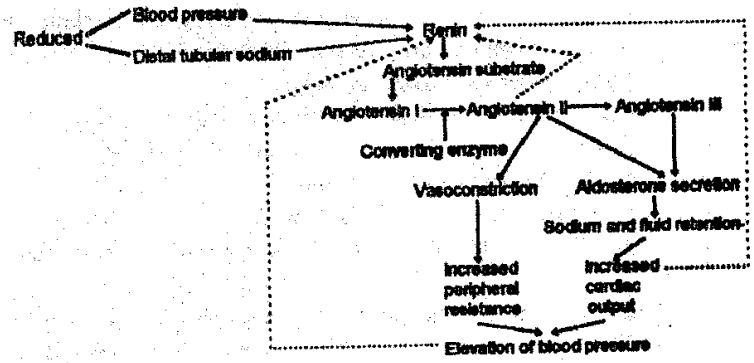


Figure no. 22
The renin-angiotensin system

The R-Ag system elevates BP by three mechanisms:

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This axis is antagonized by a hormone, atrial natriuretic factor, secreted by specialized cells in the atria.

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2. Sodium homeostasis. The kidney is intimately involved in the complex process of sodium homeostasis. One mechanism already discussed in the renin-angiotensin system, which affects distal tubular absorption of sodium, through mediation of aldosterone secretion.

Two other renal factors have important bearing on sodium homeostasis: the GFR and GFR-independent natriuretic factors. When blood volume is reduced, the GFR falls; this in turn leads to increased reabsorption of sodium by proximal tubules in an attempt to conserve and expand blood volume. Such GFR-independent factors include atrial natriuretic factor or atriopeptin, a group of peptides secreted by heart atria in response to volume expansion, which inhibits sodium reabsorption at distal site.

3. **Renal vasodepressor substances**. The kidney produces a variety of vasodepressor or antihypertensive substances, which presumably counterbalance the vasopressor effects of angiotensin. The vasodepressor substances include the prostaglandins, an urinary kallikrein-kinine system, platelet-activating factor and nitric oxide / EDRF (endothelin-derived relaxation factor).

HT cane be induced in dogs by surgical reseaction of large amount of kidney tissue, followed by incresed Na^+ and water intake. CO, and therefore BP, is rapidly increased as a result of the rapid change in blood volume.

Within a few days, hawever pressure-induced diuresis results in return to near-normal CO and plasma volume. At this point, BP is maintained by increased peripheral resistance.

Even though we know that the elevation in pressure was initialy due to increased volume, compensatory mechanisms mask the volume changes and cause apparent primary hypertension.

It is possible that mary cases of human primary HT, in much the same mamer, represents an end stage of process that begins with alterations in CO, salt metabolisme, or atrial natriuretic factor.

Etiopathogeny

Main causes and possible factors in the pathogenesis of HT:

In about 90% of cases, HT is idiopathic and apparently primary (ESSENTIAL HYPERTENSION); of the remaining 10%, most is SECONDARY to **renal disease** or, less often, to narrowing of the renal artery, usually by a atheromatous plaque (renovascular hypertension) and relatively infrequent is secondary to **endocrine disorders** (oral contraceptives, primary aldosteronism, Cushing's syndrome, pheochromocytoma) and **coarctation of the aorta**.

Essential hypertension (90%)

Genetic defect in renal sodium excretion

Genetic defect in sodium / calcium transport in vascular smooth muscle

Increased vasoconstrictive influences: behavioral, neurogenic, hormonal

Secondary hypertension (10%)

Renal disease: increased renin secretion, sodium and fluid retention, decreased vasodilator (vasodepressor) secretion

Endocrine causes: aldosteronism, oral contraceptives, pheochromocytoma, thyrotoxicosis

Vascular causes: coarctation of the aorta, vasculitis

Neurogenic causes: psychogenic, increased intracranial pressure.

Both essential and secondary HT may be either benign or malignant, according to the clinical course.

In most cases, HT remains fairly stable over years to decades and, unless a miocardial infarction or cerebro-vascular accident supervent, is compatible with long life. This form of the disorder, termed **benign hypertension**, produces a renal lesion known as benign nephroangiosclerosis. Although a benign course is most characteristic of idiopathic or essential Ht, it may also be seen with the secondary disorders.

About 5% of hypertensive persons show a rapidly rising blood pressure, which, untreated, leads to death within a year or two. Appropriately enough, this is called **accelerated or malignant HT** and the corresponding renal lesion is malignant nephroangiosclerosis. This full-blown **clinical syndrome** of malignant HT includes:

- severe HT (a dyastolic pressure over 120 mm Hg)
- renal failure
- bilateral retinal hemorrhages and exudates with or without papilledema.

This form of HT may develop in previuosly normotensive persons or it may be superimposed on preexisting benign HT, either essential or secondary. In its pure form, malignant HT usually affects younger persons that feature benign hypertension. Tipically, it develops in the 4-th decade.

Mechanisms of essential hypertension

We come now to the vexing problem of the pathogenesis of essential HT. At the outset, it is obvious from the term "essential" that the cause is unknown. At the most elemental level, it must relate to either a primary increase in cardiac output or an increase in peripheral resistance, and several theories of the origin of HT stress one or other event.

The sympatetic nervous system and the renin- angiotensin- aldosteron system have received the most attension, since both can increase CO and TPR.

In HT pressure baroreflexis tend to sustain rather than counteract hypertension, a fenomen known as "resetting the barostats", but this could be a result rather than a cause of HT. Some HT have defective storage of norepinefrine, this permitting more to circulate.

Those who advocate a primary increase in cardiac output suggest the basic non-structural, probably genetic defect, is reduced renal sodium excretion in the presence of normal arterial pressure (defective pressure natriuresis). Decreased sodium excretion would lead to an increase in fluid volume and rise in cardiac output. In the face of increasing cardiac output, peripheral vasoconstriction occurs to prevent overperfusion of tissues, which would result from an unchecked increase in cardiac output. This process, called autoregulation, leads to increased peripheral resistance and along with it an elevation of blood pressure. At the higher setting of blood

pressure, enough additional sodium can be excreted by the kidneys, to equal intake and prevent fluid retention. Thus, an altered but steady-state of sodium excretion is achieved ("resetting of pressure natriuresis").

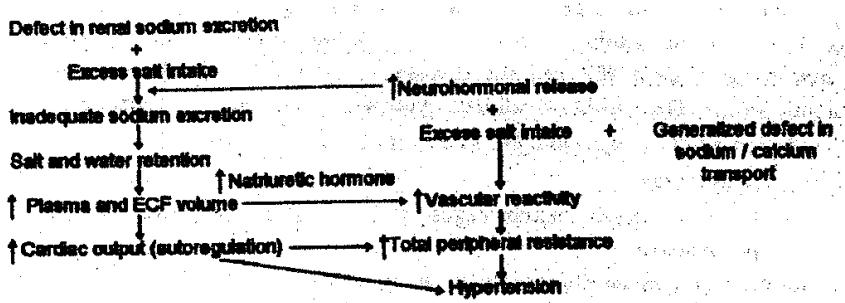


Figure no. 23

Hypothetical scheme for pathogenesis of essentiale HT implicated genetic defects in renal sodium excretion, or in sodium/ calcium tansport, or causing incraesed neurohormonal release- coupled with excess salt intake. Increased CO and TPR contribute to the HT.

The second hypothesis implicates vasoconstrictive influences as primary events. This could be (1) behavioral or neurogenic factors, as shown by the reduction of blood pressure that can be achieved by mediation (relaxation response); (2). Increase release of vasoconstrictor agents (e.g. renin, cathecolamines, endothelin); (3). A primary increased sensitivity of vascular smooth muscle, caused by a genetic defect in cell membrane transport of sodium and calcium, leading to increased intracellular calcium and contraction in the smooth muscle cells. Abnormal natrium transport across the cell wall due to a defect in or inhibition of the Na-K pump (Na-K ATP-ase) or because of increased permeability to the sodium ion, has been described in some forms of human HT and also in animal studies. The net result is increased intracellular sodium, which makes the cell more sensitive to sympathetic stimulation.

Since Ca follows Na, it is postulated that the accumulation of intracellular calcium (and not Na per se) is responsible for the increased sensitivity. Defects in sodium transport have been described in normotensive children of HT parents. This leads to increased total peripheral resistance. HT may result from deficiency of a vasodilator substance rather than excess of a vasoconstrictor. The kallikrein system, which produces the potent vasodilator bradikinin, is beginning to be studied. It is

recognized that extracts of renal medulla contain vasodilator substances, including a neutral lipoid and a prostaglandin; their absence, due to renal parenchymal disease or bilateral nephrectomy would permitt BP to rise.

Both hereditary and environmental factors have been implicated in HT. When both parents are hypertensive, the children have a much increased risk of developing HT. Studies on twins and familial aggregations support a role for the genetic constitution in the causation of HT. If heredity is involved, **how is the genetic defect manifested?** Defects related to renal sodium:

- renal sodium reabsorption or
- sodium and calcium transport in vascular smooth muscle

have been suggested, which could lead to HT by the mechanisms described previously. Even if genetic predisposition to HT exists, it is likely that environmental factors are also involved in the expression of the genetic abnormalities. The role of environment is ilustrated by the lower incidence of HT in chinese people living in their native country as compared with persons of chinese descent living in the US. Environmental factors implicated in the causation of HT include stress, obesity, smoking, inactivity and heavy consumption of salt. The evidence linking the level of dietary sodium intake with the prevalence of HT in different population groups, is impressive. It must be stressed in both of the major hypothesises discussed that heavy sodium intake augments the hypertension.

Essential hypertension is thus a complex disorder that may have more than one cause. It may be initiated by a disturbance in any of the factors that controll normal BP, many of which are environmental (stress, salt intake, estrogens), but act in the genetically predisposed individuals. In established HT, both increased BP and increased peripheral resistance contribute to the increased pressure.

THE MOSAIC THEORY states that the recruitement of multiple factors sustains elevated BP even though an aberation of only one was initially responsible; eg the interaction between the sympathetic nervous system and the R-Ag-Ald system. Sympathetic inervation of JGA in the kidney release renin; Ag II stimulates autonomic centers in the brain to increase sympathetic discharge. Ag II also stimulate production of Ald, which leads to Na enhances the reactivity of avscular smooth musccle to sympathetic stimulation. This is why it is so difficult to separate the relative role of R-Ag- Ald system and the autonomic nervous system in the genesis of primary HT

Secondary hypertension

In 5 - 10% of patients with HT, the HT is secondary to a definitely diagnosticable disease; secondary HT represent a continuous elevation of blood pressure resulting from a primary disease process.

I. RENAL DISEASE

From the point of view of pathogenesis, two categories of renal hypertension can be recognized: those asociated with excessive renin secretion (e.g., renovascular hypertension) and those associated with volume excess (e.g., acute GN). In some cases of chronic renal failure a mixture of both patterns is seen. Experimental models developed by Goldblatt clearily demonstrate these two mechanisms and have greatly helped our understanding of renal hypertension. Renal ischaemia, produced by clamping one renal artery (the so-called Goldblatt kidney) leaving the other kidney intact, produces hypertension that is mediated by excessive release of renin.

1. Renovascular HT involves obstruction of renal blood flow at the level of the renal artery. The affected kidney interprets this obstruction as volume depletion and inadequate cardiac output. This stimulates the renin-angiotensin system, causing an increase in circulating angiotensin, the retention of sodium and water, and thus HT.

Renovascular HT occurs due to atherosclerotic involvement of the renal arteries in elderly patients or due to fibromuscular disease of the renal artery in young women. Renovascular HT may be suspected where the hypertension is persistent and difficult to controll.

2. Renal parenchymal diseases. Diseases that reduce kidney function often produce HT. HT probably occurs because of the kidney's inablility to excrete sodium and water properly (the activation of renin-angiotensin mechanism also may be responsible). Since most renal diseases are not directly reversible, therapy for HT in these conditions is the same as for primary HT.

Renal hypertension is most likely to respond to drugs that interfere with the renin-angiotensin axis; however, the treatment of choice in renal arterial HT is reconstruction of the artery. When vascular 'reconstruction is performed or the affected kidney is removed, blood pressure may return to normal, especially if the HT is of recent origin. The procedure is less successful in long standing HT, because the controlateral kidney damaged by HT also begins to release excessive amounts of renin, and because other less well understood mechanisms for the perpetuation of HT take over.

Activation of the renin-angiotensin system has also been implicated in the pathogenesis of HT associated with polyarteritis nodosa, unilateral chronic pielonephritis, juxtaglomerula cell tumors, malignant Ht and chronic renal disease.

II. ENDOCRINOLOGIC CAUSES

1. Oral contraceptives cause HT in about 5% of patients who use them. HT occurs due to stimulation of renin-angiotensin system by the estrogens in the pill. Estrogens stimulate angiotensin synthesis and increase vascular angiotensin II receptor. The HT is reversed by discontinuing use of the oral contraceptives.

2. Primary aldosteronism. Mineralocorticoid excess produced by adrenal adenoma, Conn's syndrome or by stimulation of the adrenal gland by an unknown mechanism leads to HT due to retention of natrium and water, promoted by excess aldosterone. This syndrome is also complicated by hypokalemia. Patients with solitary adenoma should undergo resection of the tumor while patients with bilateral adrenal hyperplasia are treated with spironolacton.

3. Cushing's syndrome. Glucocorticoid excess due to exogenous glucocorticoid therapy, a pituitary tumor or an adrenal adnoma produces HT in about 80% of patients who have the syndrome. HT occurs because cortisole has mineralo-corticoid effects and, therefore, leads to the retention of sodium and water.

Additionally, ACTH or corticotropin (CRF) may stimulate the R-Ang system.

Cushing's syndrome usually can be suspected in patients with a history of taking exogenous glucocorticoid and in those with a cushingoid appearance. In patients not taking exogenous glucocorticoids, the syndrome can be confirmed by the measurement of either plasma cortisole or urinary 17- hydroxicorticoids.

4. Pheochromocytoma. This tumour of the adrena medula produces an increased secretion of catecholamines, leading to HT. Approximately 50% of patients have episodic HT.; the remaining 50% have conctant HT. Episodes of flushing, diaphoresis, weight loss, and diarrhea may suggest the diagnosis. Measurement of urinary catecholamines and catecholamine metabolites , including metanephrine and vanillylmandelic acid also is usefull in making the diagnosis. The tumour may be located in the adrenal medulla by the use of computed tomography.

5. Miscellanous causes. Acromegaly, hyperparathyroidism and hyperthyroidism also may produce HT.

III. VASCULAR CAUSES

Coarctation of the aorta is a stenosis of the aorta, usually at the site of the ductus arteriosus. If severe, the stenosis limit aortic blood flow distal to the constriction. If the coarctation does not cause heart failure due to pressure overblood in childhood, it may not be detected until it presents as HT in the adult; the kidneys are perfused at a subnormal blood pressure. Some investigates have found elevated renin levels and activation of the renin- angiotensin system in adult with coarctation, while helps to explain the HT.

Blood pressure determined in the arms usually is elevated , whereas pulses in the legs are reduced or absent.; the upper body usually is wel developed , while the legs appear underdeveloped.

IV. NEUROGENIC CAUSES

Psychogenic, increased intracranial pressure.

Malignant hypertension and malignant nephrosclerosis

Malignant HT is far less common than benign HT, occuring in only about 5% of patients with elevated BP. It may arise de novo (i.e. without preexisting HT) or appear suddenly in a person who had mild HT. The basis for this turn for the worse in HT subject is unclear, but the following sequence of events is suggested. The initial event appears to be some form of vascular damage to the kidneys. This most commonly results from long standing benign HT with eventual injury to the arteriolar walls or it may spring from arteritis. In either case, the result is increased permeability of the small vessels to fibrinogen and other plasma proteins, endothelial injury and platelet deposition. This leads to the appearance of the fibrinoid necrosis of arterioles and small arteries, and intravascular thrombosis. Mitogenic factors from platelets (e.g. PDGF) and plasma cause intimal smooth hyperplasia of vessels, resulting in the hyperplastic arteriosclerosis typical of malignant HT and further narrowing of the lumens. The kidneys become markedly ischaemic. With severe involvement of the renal afferent arterioles, the renin-angiotensin system receives a powerful stimulus, and indeed patients with malignant HT have markedly elevated levels of plasma renin. This then sets up a self-perpetuating cycle in which angiotensin II causes intrarenal vasoconstriction and the attendant renal ischaemia perpetuates renin secretion. Aldosterone levels are also elevated, and salt retention undoubtedly cotributes to the elevation of BP. The consequences of the markedly elevated BP on the blood vessels through the body is known as malignant arteriosclerosis and the renal disorder as malignant nephrosclerois (MNS).

The full-blown syndrome of malignant HT is characterized by dyastolic pressures greater than 120 mm Hg, papilledema, encephalopathy, cardiovascular abnormalities and renal failure. Most often, the early symptoms are related to increased intracranial pressure and include headaches, nausea, vomiting and visual impairments, particularly the developement of scotomas or spots before the eyes. At the onset of rapidly mounting BP there is marked proteinuria and microscopic, or sometimes macroscopic, hematuria, but no significant alteration in renal function. Soon, however, renal failure makes its appearance. The syndrome is a true medical emergency that requires the prompt institution of agressive antihypertensive therpy before that irreversible renal lesions develop. About 50% of patients survive at least 5 years, and further progress is still being made. 90% of death are caused by uremia and other by cerebral hemorrhage or cardiac failure.

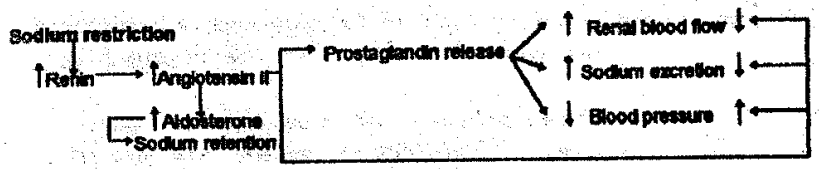


Figure no. 24
The side effects of sodium restriction during HT therapy.

Complications

Untreated HT damages the small arterioles resulting in stroke, myocardial infarction, congestive heart failure, renal failure and encephalopathy.

Hypertensive heart disease (HHD). The minimal anatomic criteria for the diagnosis of HHD are: (1) a history of HT and (2) left ventricular hypertrophy in the absence of other conditions that might induce it (e.g. aortic valve stenosis, aortic coarctation). Idiopathic asymmetric septal hypertrophy, which may mimic the morphologic changes of HHD, must also be ruled out on clinical grounds (e.g. no history of HT, younger age). In HT, the stimulus to hypertrophy is pressure overload. The stress leads to production within myocytes of new myofilaments, myofibrils, mitochondria and ribosomes and to a switch in the type of myosin synthesized.

II.2.5. Pathophysiology of arterial (orthostatic) hypotension

Definition: an excessive fall in BP, on assuming the upright posture, typically more than 20/10 mm Hg. It is not a specific disease, but rather a manifestation of abnormal BP regulation due to a variety of causes.

Etiology and pathophysiology: Sudden standing results in pooling of the blood in the capacitance veins of the legs and trunk, with subsequent transient decrease in venous return and CO with reduction of the BP. Normally, baroreceptors in the aortic arch and carotid bodies activate autonomic reflexes that rapidly normalize BP and cause a transient tachycardia. These changes reflect primarily the sympathetic-mediated increase in cathecolamines levels that augments vasomotor tone of the capacitance vessels, increases heart rate and myocardial contractility, and thereby enhances CO; arterial and venous vasoconstriction are mediated by similar mechanisms.Vagal inhibiton also increases heart rate. With continued standing,

antidiuretic hormone secretion and activation of the renin-angiotesin-aldosterone system cause sodium and water retention and expansion of the circulating blood volume.

If afferent, central, or efferent portions of the reflex arch are impaired by diseases or drugs, or if myocardial contractility or vascular responsiveness is depressed; if there is hypovolemia, or if hormonal responses are faulty, these homeostatic mechanisms do not restore the lowered BP anymore, with subsequent decreased tissue perfusion.

Causes:

Hypovolemia and relative hypovolemia are due respectively to excessive use of diuretic agents and vasodilator therapy with nitrate preparations, calcium antagonists or converting enzyme inhibitors

Decreased baroreceptor responsiveness, coupled with decreased arterial compliance, accounts for frequent orthostatic hypotension in elderly persons.

Drugs that impair autonomic reflex mechanisms, e.g. excessive doses of antihypertensive drugs (methyl-DOPA, clonidine, rezerpine and ganglionic blocking drugs) are also frequent causes; rarely, beta-adrenergic blocking drugs are rare causes but alpha adrennergic blocking agents may be causative as a first dose-effect. Tricyclic and tetracyclic antidepressanta, monoaminoxidase inhibitors, phenothiazine antipsychotic drugs reversibly impair autonomic reflexes and reduce BP on standing as an important adverse effect.

Hypovolemia caused by disease may produce orthostatic hypotension due to a decrease in CO despite intact autonomic reflexes. This is seen with hemorrhage, severe vomiting or diarrhoea, excessive sweating or the osmotic diuresis in uncontrolled diabetes mellitus.

Neurologic disorders that involve the autonomic nervous system interrupt the sympathetic reflex arch and impair normal adrenergic responses to standing.This is common with diabetic neuropathy, amyloidosis, porphyria, tabes dorsalis, syringomyelia, spinal cord transection, Guillain-Barre syndrome.

Shy-Drager syndrome and idiopathic orthostatic hypotension are two possibly related primary neuropathic disorders commonly associated with with severe hypotension; they both display widespread lesions of the sympathetic and parasympathetic nervous systems, basal ganglia and spinal tracts, with resultant widespread autonomic dysfunction additional to the failure of arterial and venous vasoconstriction. In Shy-Drager syndrome, plasma norepinephrine does not increase on standing; in idiopathic orthostatic hypotension there appears to be depletion of norepinephrine from the sympathetic nerve endings.

Symptoms, signs and diagnosis

Faintness, light- headedness, dizzeness, confusion or visual blurring is evidence of a mild to moderate reduction in cerebral blood flow. With more severe cerebral

hypoperfusion , syncope and generalized seizures may supervene. Exercise or a heavy meal may exacerbate the symptoms. Other phenomena associated wuth the orthostatic hypotension usually relate to the underlying cause.

The diagnosis of orthostatic hypotension is made when symptoms suggestive of hypotension and a marked reduction in measured BP are provoked by standing and relieved by lying down. However, an underlying etiology must be sought , based on each patient's presenting circumstances and associated phenomena.

II.2.6. PATHOPHYSIOLOGY OF HEART FAILURE

Definition

Heart Failure (HF) is a clinical syndrome with many different etiologies (cardiac and extracardiac diseases) that reflects a fundamental abnormality in effective mechanical performance of the heart, resulting in cardiac output (CO) inadequate to meet the body's needs.

Cardiac failure may be manifest by:

A. a decrease in cardiac output and/or

B. a damming of blood in the veins behind the left or right side of the heart - even though the cardiac output may be normal or, at times, above normal.

Impaired cardiac function may be manifested initially only during exertion, but with progression of disease, the contractile performance of the heart deteriorates, and symptoms and signs of congestion and fatigue are associated with a low CO, even at rest.

1. Factors which determine The heart performance

The clinical findings and treatment of heart failure can be best understood by first reviewing normal cardiac function and the effects of disease. At rest and during exercise, CO, venous return, and distribution of blood flow, with O_2 delivery to the tissues, are balanced by neurohumoral and intrinsic cardiac factors, to meet the body's needs. Factors that influence contraction of the isolated papillary muscle and determine left ventricular performance and myocardial O_2 requirements, include preload, contractile state, afterload, rate of contraction, substrate availability, and the extent of tissue damage. The energy of cardiac muscle contraction and resultant systolic cardiac performance is proportional to the degree of stretch of the myocardial fiber at end-diastole.

1. The preload (venous return) or the tension on the relaxed myocardial fiber when it begins to contract is influenced by the end-diastolic volume and pressure and

the thickeness of the myocardial wall. The resultant force per cross-sectional area of the myocardial fiber is referred to as the **end-diastolic stress.**

Acutely, end-diastolic volume and wall thickness often remain unchanged and therefore the end-diastolic pressure is a reasonable reflection of preload.

Chronically, left ventricular dilation and hypertrophy modify end-diastolic stress by modifying the volume and the wall thickness. Changes in myocardial distensibility or compliance also influence preload.

2. The contractile state in the isolated muscle is characterized by the *force and velocity of contraction*. The overall contractile state clinically is often expressed as the ejection fraction (the left ventricular stroke volume as a percent of the left ventricular end-diastolic volume). The heart has an built-in mechanism to adapt to changing volumes of inflowing blood called the Franck-Starling mechanism of the heart. Basically, the Franck-Starling mechanism means that the greater the heart muscle is stretched during filling, the greater will be the force of contraction and the greater will be the quantity of blood pumped into the aorta. Or another way to express this is: within physiological limits, the heart pumps all the blood that comes to it without allowing excessive damming of blood in the veins.

The pumping effectiveness of the heart is highly controlled by the sympathetic and parasympathetic stimulation. The sympathetic stimulation increases the force with which the heart muscle contracts, therefore increasing the volume of blood pumped and increasing the ejection pressure. Strong vagal stimulation can decrease the strength of heart contraction by 20 to 30 per cent.

Physiological cardiac function can be described in terms of the ventricular function curve. It results that at any given right atrial pressure, the cardiac output increases with increasing sympathetic stimulation and decreases with increasing parasympathetic stimulation.

1. The after-load (out flow resistance), or the force resisting myocardial fiber shortening after stimulation from the relaxed state, is determined by the chamber pressure, volume, and wall thickness at the time of aortic valve opening. This is the load or resistance against which the ventricle contracts. Clinically, afterload is equated to **systemic blood pressure** at the moment of aortic valve opening or shortly after, as peak systolic wall stress.

2. The heart rate is the first to vary when the cardiac output has to adapt to new demands. In general, the more times the heart beats per minute, the more blood it can pump, but there are important limitations of this effect. For instance, once the heart rate rises above a critical level, the heart strength itself decreases, presumably because of overuse of metabolic substrates in the cardiac muscle. In addition, the period of diastole between the contractions becomes so reduced that blood does not have time to flow adequately from atria into the ventricles. For this reason, when the heart rate is increased artificially by electric stimulation, the heart reaches its peak ability to

pump large quantities of blood at a rate between 100 and 150 beats per minute. On the other hand, when its rate is increased by sympathetic stimulation, it reaches its peak ability to pump blood at a heart rate between 170 and 220 beats per minute. The reason for the difference is that sympathetic stimulation not only increases the heart rate but also increases the heart strength. At the same time it decreases the duration of systolic contraction and allows more time for filling during diastole.

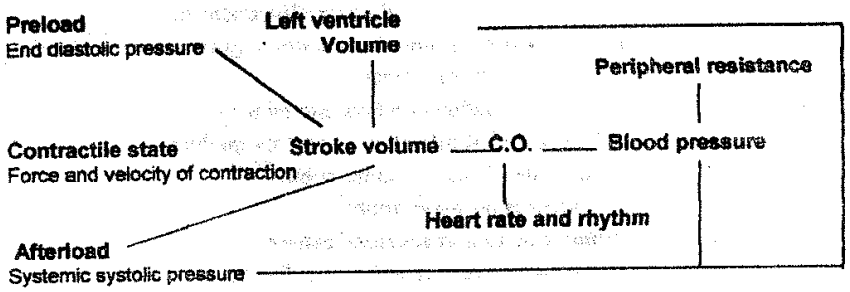


Figure no. 25
Interrelations between myocardial function determinants

Substrate availability and **tissue damage** are additional influences on myocardial performance, in both the isolated muscle and the intact left ventricle. Reduction in O2 availability and changes in major substrate availability (e.g., fatty acid, glucose) can impair and reduce the vigour of cardiac contraction and performance. Tissue damage, either acutely with myocardial infarction or chronically with fibrosis resulting from tissue injury, not only impairs local myocardial performance but also imposes an additional burden on viable myocardium.

2. Causes of heart failure

Basically, the heart failure result as a consequence of one or more of the folowing main mechanisms: impaired contraction, excess work demands, and inadequate filling. However, the pathogenesis is more complicated, especially in the case of decompensation. From this standpoint, there are **underlying causes** and **precipitating causes** of heart failure. The underlying causes are primary causes. They may exist for many years and produce no clinical disability. Frequently, the manifestation of clinical heart failure appears for the first time in the course of some acute disturbances which places an additional load on a myocardium that chronically is excessively burdened and while compensated has no functional reserves, resulting in further deterioration of cardiac function. The identification of such precipitating causes is of critical importance because their prompt alleviation may be lifesaving.

However, in the absence of underlying heart disease these acute disturbances do not usually, by themselves, lead to heart failure.

2.1. UNDERLYING CAUSES

There are mainly three mechanisms which may primarily impair the heart function:

* **Excess work demands**: cardiac pressional or hypervolemic overburden
  - **increased pressure work** e.g. systemic hypertension, aortic stenosis, pulmonary hypertension
  - **increased volume work** e.g. mitral and aortic regurgitation, ventricular septal defect
* **Pump failure** contractile dysfunction (systolic failure) e.g. myocardial infarction, cardiomyopathies
  inadequate filling (diastolic failure) e.g. ventricular hypertrophy
* **Inadequate heart filling due to extracardiac causes** e.g. constrictive pericarditis, cardiac tamponade

2.2. PRECIPITATING CAUSES

Cardiac factors

- inflammatory causes: rheumatic and other forms of myocarditis, infective endocarditis
- negative inotropic agents (beta blockers, calcium channels blockers, antiarrhytmics)
- myocardial ischemia
- arrhythmias and blocks
- acute mechanic injuries

Extracardiac factors

- systemic or pulmonary hypertension
- hypervolemia
- hyperkinetic states (anemia, thyrotoxicosis, fever, pregnancy)

3. Compensatory mechanisms in heart failure

The compensatory mechanisms are immediate and late, central and peripheral.

- **Immediate mechanisms**
  1. Central
     - tachycardia
     - heart dilation
  2. Peripheral
     - redistribution of cardiac output
     - increased hemoglobin desaturation
- **Late mechanisms**
  1. Central
     - hypertrophy
  2. Peripheral
     - renal retention of fluid

3.1. CENTRAL COMPENSATORY MECHANISMS

Cardiac reserve may be defined as unutilised ability of the resting heart to deliver O_2 to the tissues

- ***Increased heart rate.*** Tachycardia is the most quick to act compensatory mechanism. It is mainly the result of the sympathetic stimulation. Above a certain threshold, tachycardia increases the oxygen consumption and reduces the diastolic filling and the stroke volume.
- ***Heart dilation.*** The Franck -Starling mechanism relates the myocardial muscle stretch to the inotropic state of the myocardium. An increased stretch results in an increased force of contraction.
- ***Cardiac hypertrophy.*** Myocardial hyperfunction induces increased myocyte size (cellular hypertrophy through addition of sarcomeres) that causes an increase in the overall mass and size of the heart. The diameters of the cardiac myocytes can increase from the normal 15 mm to 25 mm or more in hypertrophy. Because adult cardiac myocytes cannot divide, augmentation of myocyte number (hyperplasia) cannot occur in the adult heart.

The pattern of hypertrophy reflects the stimulus. Pressure-overloaded ventricles (e.g. hypertension or aortic stenosis) develop concentric hypertrophy with an increased ratio of wall thickness to cavity radius. In contrast, volume-overloaded ventricles (e.g. mitral regurgitation) develop hypertrophy with dilatation (eccentric hypertrophy), with proportionate increases in ventricular radius and wall thickness.

3.2. PERIPHERAL COMPENSATORY MECHANISMS

1. Redistribution of cardiac output. The redistribution of cardiac output serves as an important compensatory mechanism when the patient with heart failure exercises, but as heart failure advances, redistribution occurs even in the basal state. Blood flow is redistributed so that the delivery of oxygen to vital organs, such as the brain and the myocardium, is maintained at normal or near-normal levels, while flow to less critical areas, such as the cutaneous and muscular beds and splachnic viscera,

is reduced. Vasoconstriction mediated by the sympathetic nervous system is largely responsible for this redistribution, which in turn may be responsible for many of the clinical manifestations of heart failure. such as fluid accumulation (reduction of renal blood flow), low-grade fever (reduction of the cutaneous flow), and fatigue (reduction of muscle flow).

*2. **Renal retention of fluid and increase in blood volume.*** A moderate increase in body fluid and blood volume is an important factor in compensating the diminished pumping ability of the heart because it increases the tendency for venous return. The increased blood volume increases the tendency for venous return in two ways:

- It increases the pressure gradient for causing flow of blood toward the heart
- It distends the veins, which reduces the venous resistance and thereby allows increased ease of blood flow to the heart.

*3. **Increased peripheral hemoglobin desaturation*** is due to the decreased affinity of hemoglobin for oxygen. This is duc to tissular acidosis, increased red cell 2.3-diphosphoglicerate and decreased velocity of capillary circulation. The result is an abnormal widening of arterial-venous oxygen difference and peripheral cyanosis.

4. Neuroendocrine regulation of the compensatory mechanisms

A coordinated response governed by the neuroendocrine system is necessary for an efficient compensation. There are local and general, vasoconstrictory and vasodilatory mechanism which take part to this adaptive response.

The main systems involved are as follows:

- **Vasoconstrictory**: sympathetic stimulation, renin-angiotensin-aldosterone system, ADH (antidiuretic hormone)
- **Vasodilatory**: atrial natriuretic peptide, nitric oxide, prostaglandins

The stimuli which trigger the intervention of these systems are the resultant hemodinamic changes that occur in heart failure. A change in the vascular cell metabolism makes the translation of the hemodinamic events into molecular events. Specialised structures as such as the baroreceptors and the chemoreceptors are also involved. The vasoconstrictor response predominates There is an attempt to compensate for the decreased effective blood flow by heart stimulation, vasoconstriction, redistribution of the blood flow, and an increased in the circulate volume by renal salt and water retention.

1. The sympathetic stimulation is triggered by baroreceptor-mediated reflexes. It determines central and peripheral effects as well:

Central effects:

- tachycardia
- increased contractility
- increased diastolic relaxation

Peripheral effects:

- selective vasoconstriction and flow redistribution
- renin release

The level of plasma catecholamines stands for the severity of the cardiac dysfunction, and is correlated with the prognosis of the disease. In spite of increased plasma catecholamines their myocardic efficiency is reduced perhaps as a result of receptor down-regulation.

2. The renin-angiotensin-aldosterone system

The decrease in the afferent arteriole blood flow as a result of a fall in cardiac output, and the subsequent renin release from macula densa results in vasoconstriction and salt and water retention as a result of angiotensin II formation and aldosterone release (see salt and fluid retention in heart failure).

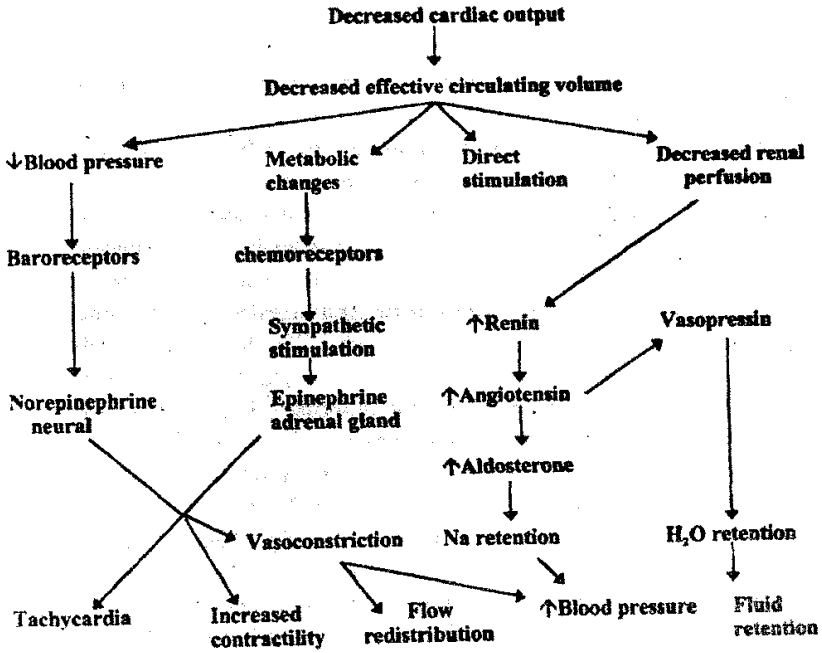


Figure no. 26

The compensatory mechanisms triggered by a decrease in cardiac output

3. The antidiuretic hormone also contributes to fluid retention as a consequence of its action on the distal convoluted tubule.

4. The prostaglandines are both vasoconstrictive and vasodilatory depending on the species of prostaglandine which is released and the territory it acts on. They are co-effectors of the regional flow redistribution.

5. *The atrial natriuretic peptide* is released as a result of atrial distension secondary to the fluid retention. It promotes vasodilatation, increased diuresis and natrium excretion, and also decreased renin and norepinephrine release.

5. Dinamics of adaptive mechanisms in cardiac failure: from compensation to decompensation

5.1. Acute compensation

A deficiency of the contractile state initiates the sequence of events that eventually lead to the clinical manifestation of HF, i.e. myocardial infarction. As a result, two essential effects occur:

(1) reduced cardiac output and

(2) damming of blood in the veins, resulting in increased systemic venous pressure.

The low cardiac output is still sufficient to sustain life for perhaps a few hours, but it is likely to be associated with fainting. This acute stage usually lasts for only a few seconds because of the sympathetic reflexes that can compensate, to a great extent, for the damaged heart. The baroreceptors are activated by the diminished arterial pressure and strong sympathetic stimulation occurs. This has two major effects: first, on the heart itself and, second, on the peripheral vasculature. The normal muscle is strongly stimulated by sympathetic stimulation, in this way partially compensating for the non-functional muscle. The heart becomes a stronger pump, often as much as 100 per cent stronger, under the influence of the sympathetic impulses. Tachycardia helps to maintain the cardiac output.

Sympathetic stimulation also increases the tone of most of the blood vessels of the circulation, especially the veins, raising the main systemic filling pressure to 12 to 14 mmHg, almost 100 per cent above normal, which increases the tendency of blood to flow back to the heart. Therefore, the damaged heart also become primed with more inflowing blood than usual, the left ventricular end-diastolic pressure or preload will increase and will shift the ventricular function curve to the right (Frank-Starling mechanism), further increasing the ventricular force of contraction. Systemic BP is maintained by a compensatory increase in peripheral vascular resistance. Blood

redistribution and increased peripheral desaturation of hemoglobin may also occur depending on the severity of the heart failure.

5.2. Chronic compensation

After the first few minutes of an acute heart attack, a prolonged secondary state begins, characterized mainly by two events: (1) retention of fluid by the kidneys and (2) usually progressive recovery of the heart over a period of several weeks to months. The beneficial effect of moderate fluid retention in cardiac failure has been discussed.

6. Salt and water retention: pathophysiology of cardiac edema

When the volume of blood pumped by the left ventricle into the systemic vascular bed is chronically reduced the effective arterial blood volume is reduced and as a consequence a series of physiologic responses designed to restore it to normal are set into motion. The urine output decreases and fluid retention develops. There are three known causes of the reduced renal output of urine during cardiac failure:

1. Decreased glomerular filtration

A decrease in cardiac output has a tendency to reduce the glomerular pressure in the kidneys because of:

- reduced arterial pressure and
- intense sympathetic constriction of the afferent arteriole of the kidney

As a consequence, the glomerular filtration rate becomes less than normal. Even a slight decrease in glomerular filtration rate often markedly decreases the urine output. When the cardiac output falls to about one-half normal, this can result in almost complete anuria.

2. Activation of the Renin-Angiotensin System

The reduced blood flow to the kidneys causes marked increase in renin output, and this in turn causes the formation of angiotensin which acts directly on the arterioles of the kidneys to further decrease the blood flow through the kidney. Therefore, the net loss of water and salt into the urine is greatly decreased, so that the quantities of salt and water in the body fluids increase.

3. Increased aldosterone secretion

This results mainly from the effect of angiotensin on the adrenal cortex. The elevated levels of aldosterone further increase the reabsorption of sodium from the renal tubules, and this in turn leads to a secondary increase in water reabsorption for two reasons. First, as the sodium is resorbed, it reduces the osmotic pressure in the tubules while increasing the osmotic pressure in the renal interstitial fluids; these

changes promote osmosis of water into the blood. Second, the absorbed sodium and anions to go with it, mainly chloride ions, increase the osmotic concentration of the extracellular fluid everywhere in the body, and this elicits antidiuretic hormone secretion by the hypothalamic-posterior pituitary system. The antidiuretic hormone then promotes a still greater increase in tubular reabsorption of water.

Atrial Natriuretic Factor (ANF) has the capacity to oppose sodium retention and blood pressure elevation in the states characterised by hypervolemia. ANF acts by increasing the excretion of sodium and water and by arteriolar and venous dilatation. However, its effectiveness seems to be reduced in advanced congestive heart failure, as long as these patients have low rates of sodium excretion despite often having high circulating levels of ANP.

In some instances of mild heart failure, a small increment of total blood volume may repair the deficit of arterial volume and establish a new steady state as long as the previously described compensatory mechanisms accounts for the return of the cardiac output towards normal. However, if the cardiac disorder is more severe, retention of fluid cannot repair the deficit in effective arterial blood volume. The evolution of heart failure becomes a downward spiral towards decompensation.

Decompensated heart failure

If the heart becomes severely damaged, no amount of compensation, either by sympathetic nervous reflexes or by fluid retention, can make the weakened heart pump a normal cardiac output. As a consequence, the cardiac output cannot rise to a high enough value to bring about return of normal renal function. Fluids continues to be retained and this begins to have serious physiological consequences; overstretching of the heart, thus weakening the heart still more, filtration of fluid into the lungs to cause pulmonary edema and consequent deoxygenation of the blood, and development of extensive edema in all the peripheral tissues of the body.

Thus, the main basis of decompensated heart failure is failure of the heart to pump sufficient blood to make the kidneys excrete daily the necessary amounts of fluid.

The structural/biochemical/molecular basis for myocardial contractile failure is obscure in many cases. In some instances (myocardial infarction), there is obvious death of myocytes and loss of vital elements of the 'pump'; the remaining, noninfarcted regions are overworked. In contrast, in valvular heart disease, increased pressure or volume work affects the chamber wall globally. The increased myocyte size that occur in cardiac hypertrophy is usually accompanied by decreased capillary density, increased intercapillary distance, and deposition of fibrous tissue.

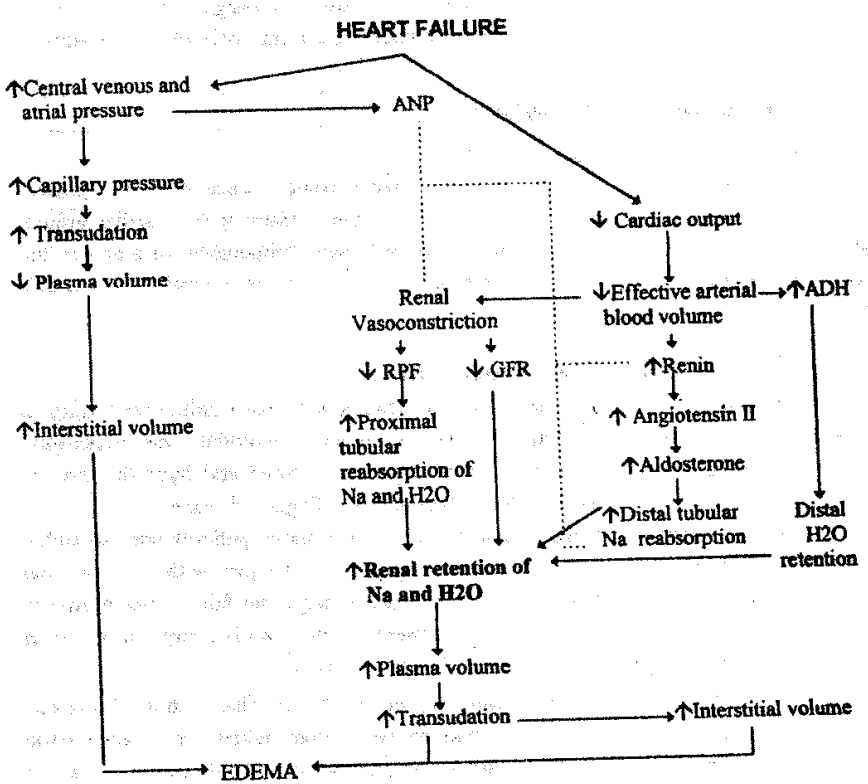


Figure no. 27
Sequence of events in compensated and decompensated HF. (RPF - renal perfusion rate; GFR - glomerular filtration rate)

Moreover, the molecular changes in hypertrophied hearts that initially mediate enhanced function may contribute to the development of the heart failure. With prolonged hemodynamic overload, gene expression is altered, leading to re-expression of a pattern of protein synthesis analogous to that seen in fetal cardiac development; other changes are analogous to events that occur during mitosis of normally proliferating cells. Thus, proteins related to contractile elements, excitation-contraction coupling, and energy utilization may be significantly altered through production of different isoforms that either may be less functional than normal or may reduced or increased in amount. Other proposed but not established mechanisms

potentiating congenital heart failure include reduced adrenergic drive, decreased calcium availability, impaired mitochondrial function, and microcirculatory spasm.

7. Forms of cardiac failure

7. 1. Acute versus chronic heart failure

Heart failure can be acute but is more often chronic. **Acute failure** is present when cardiac output is grossly reduced, such as after a massive myocardial infarct. **Chronic failure** develops when the heart can no longer compensate for a defect that has been present for some time. Defects of cardiac valves as a result of rheumatic fever can cause failure of this type.

7.2. High output versus low output heart failure.

The cardiac output is often depressed in patients with heart failure secondary to ischemic heart disease, hypertension, cardiomyopathy, valvular and pericardial disease, but tends to be elevated in patients with heart failure and hyperthyroidism, anemia, pregnancy, arteriovenous fistulas, beriberi, and Paget's disease.

The normal range of cardiac output is wide, and in many patients with so-called low-output heart failure the cardiac output may actually be just within the normal range at rest (although is lower than it has been previously) and fails to rise normally during exertion. On the other hand, in the patients with so-called high-output heart failure the output may not exceed the upper limits of normal.

- Regardless of the absolute level of the cardiac output, however, cardiac failure may be said to be present when the characteristic clinical manifestations are accompanied by a depression of the curve relating ventricular end-diastolic volume to cardiac performance.

In patients whose cardiac outputs are initially high the heart is called upon to pump abnormally large quantities of blood in order to deliver the normal quota of oxygen to the metabolizing tissues. The burden placed on the myocardium by the increased flow resembles that produced by chronic regurgitant valvular lesions Sooner or later, the heart succumbs to the excessive load or impaired oxygenation; output declines and low output failure develops.

7.3. Backward versus forward heart failure

When the heart fails as a pump, there may be two direct effects on the circulation: **backward** and/or **forward failure. Backward failure** refers to signs and symptoms that arise from inadequate emptying, which allows blood to accumulate in vessels or heart chambers located behind the failing ventricles (in the lungs, when there is failure of the left ventricle and in the systemic circulation when there is failure of the right ventricle), resulting in congestion of the pulmonary and venous

systemic circulation. **Forward failure** results in impaired output of the blood into the vessels emerging from the heart.

A rigid distinction between backward and forward heart failure is artificial, since both mechanisms appear to operate to varying extents in most patients with heart failure

For example, when a large portion of the left ventricle is suddenly destroyed, as in myocardial infarction, although stroke volume is reduced, the patient may die of either acute pulmonary edema, a manifestation of backward failure, or of failure of perfusion of the systemic tissues. Sometimes both mechanism operate simultaneously. Similarly, in the case of massive pulmonary embolism, the right ventricle may dilate and the systemic venous pressure may rise to high levels (backward failure), or the patient may develop shock secondary to low cardiac output (forward failure).

7.5. Left-sided versus right-sided heart failure

HF may also be classified according to the side of the heart (right or left) that is affected. Although the initial event that leads to HF may be primarily right sided or left sided in origin, long term HF usually involves both sides. In many forms of heart disease , the clinical manifestations of HF may reflect impairment of either the left or right ventricle.

With **left ventricle (LV) failure**, CO declines and pulmonary venous pressure increases. Clinical signs are fatigue and dyspnoea on effort. Elevation of the pulmonary capillary pressure to levels exceeding the oncotic pressure of the plasma proteins (about 24 mm Hg) leads to increased lung water, reduced pulmonary compliance and a rise in the O_2 cost or the work of breathing. LV failure characteristically develops in aortic valve disease, coronary artery disease, HT and with congenital defects such as ventricular septal defect or patent ductus arteriosus with increased ventricular work load.

Right ventricular (RV) failure is most commonly caused by prior LV failure (which increases pulmonary venous pressure and eventually arterial pressure with pulmonary HT) , mitral stenosis, primary pulmonary HT , multiple pulmonary emboli, pulmonary stenosis, tricuspid regurgitation of the RV and atrial septal defect. Volume overload and increased systemic venous pressure can be seen ,e.g., in polycythemia or transfusion, acute renal failure with overhydration and obstruction of either vena cava. In these conditions myocardial function may be preserved. In RV failure, fatigue, inadequate CO and systemic venous congestion with distension of neck veins, hepatic engorgement and peripheral oedema are present.

8. Systemic effects of heart failure

The organs most severely affected are: kidneys, lungs, liver, brain, spleen.

1. Renal function. Renal blood flow and GFR are reduced in HF and blood flow within the kidney is redistributed. The filtration fraction is reduced and filtered Na is decreased but tubular Na absorption is enhanced. Decreased renal blood flow leads to increased renin release from the juxtaglomerular apparatus which converts angiotensinogen in angiotensin I and II. Angiotensin II , a potent vasoconstrictor, promotes aldosterone secretion from the adrenal glands. If plasma volume is decreased, ADH may be released. As a result of these complex endocrine and renal changes, afterload, blood volume , total body Na, and body water are increased. These alterations are compensatory, since they enhance myocardial fiber stretch by increasing ventricular volume, but they also lead directly to the congestive clinical manifestations of HF.

2. Pulmonary effects. Pulmonary venous HT and oedema resulting from LV failure significantly alters pulmonary mechanism and thereby, ventilation - perfusion relationships. Dyspnea correlates with elevated pulmonary venous pressure and the resultant increased work of breathing, although the precise cause of the subjective symptoms remains debatable. With increased pulmonary venous hydrostatic pressure exceeding the oncotic pressure of the plasma proteins, fluid extravasates into the capillaries, the interstitial space and the alveoli. Pleural effusions of HF characteristically accumulate in the right hemithorax first and latter become bilateral. Lymphatic drainage is greatly enhanced but cannot mobilize the increase in lung water. Unoxygenated pulmonary arterial blood is shunted past non-aerated alveoli, decreasing mixed pulmonary capillary PO_2. A combination of the alveolar hyperventilation due to increased lung stiffness and reduced partial pressure of alveolar O_2 (Pa O_2) is characteristic of LV failure. Thus, arterial blood gas analyses reveal an increased pH and a reduced arterial partial pressure of O_2 (Pa O_2) - respiratory alkalosis - with decreased saturation reflecting increased intrapulmonary shunting.

3. Liver function. Reduced splanchnic blood flow and increased venous pressure characteristic of HF cause decreased hepatic blood flow and liver engorgement. Moderate hepatic dysfunction commonly occurs in venous hypertension (systemic and portal) secondary to RV failure, with elevation of conjugated and unconjugated bilirubin, increased prothrombin time, and rise in hepatic enzymes (alkaline phophatase, AST = SGOT and ALT = SGPT). These enzymes elevations are usually modest, but in severely compromised circulatory states with marked reduction of CO and hypotension, central liver necrosis and the manifestations of liver failure may be severe enough to suggest hepatitis with acute

liver failure. Reduced aldosterone breakdown by the liver further contributes to fluid retention.

4. Other organs. Severe chronic venous HT has been associated with the syndrome of protein-loosing enteropathy characterized by marked hypoalbuminemia, bowel infarction, acute and chronic gastrointestinal hemorrhage and malabsorption. Peripheral gangrene in the absence of large vessel occlusion has been observed in patients with chronic markedly reduced CO. Chronic irritably and decreased mental performance may reflect severely reduced cerebral blood flow and hypoxemia in chronic low output states.

SYMPTOMS AND SIGNS

HF may produce systemic and/or pulmonary venous congestion (presenting symptoms and signs of predominantly right or left sided failure, respectively), may develop gradually, or may present suddenly as with acute pulmonary oedema.

Left ventricle failure may become apparent with undue tachycardia, fatigue on exertion, dyspnea on mild exercise (*exertional dyspnea*), and intolerance to cold. *Paroxysmal nocturnal dyspnea* and cough reflect the distribution of excess fluid with the recumbent position. *Orthopnea* is shortness of breath occurring when a person is supine or lying down. Occasionally, pulmonary venous HT and increased pulmonary fluid manifest primarily as *cardiac asthma* with bronchospasm and wheezing. Cough may be prominent, and pink tinged or brownish sputum due to blood and the presence of HF cells is common. Frank hemoptysis due to ruptured pulmonary varices is uncommon but may occur with large amounts of blood loss. Signs of chronic LV failure include diffuse and laterally displaced apical impulse, palpable and audible ventricular (S3) and atrial gallop (S4) sounds, accentuated pulmonic second sounds and inspiratory basilar rales. Right sided pleural effusion is common.

Nocturia occurs relatively early in the course of congestive HF. During the day the blood flow is redistributed away from the kidney. At night, resting in the recumbent position leads to an increase in cardiac output and blood flow to the kidneys, renal vasoconstriction diminishes and urine formation increases. *Oliguria* is a late sign of a severely reduced cardiac output.

Increased sympathetic activity, although a compensatory mechanism, is also responsible for a series of physical signs in HF. Peripheral vasoconstriction is manifested by pallor and coldness; cyanosis of the digits also occurs. Diaphoresis and tachycardia may outset.

Cardiac cachexia is a condition of malnutrition and tissue vasting that occurs in persons with end-stage of HF.

Cheyne-Stokes respirations are a form of periodic breathing with a waxing and waning of respirations interspersed with periods of apnea. This type of breathing results from a discrepancy between arterial and alveolar oxygen and CO2 levels - the

consequence of a prolonged circulation time between the heart and the respiratory center in the brain.

Acute pulmonary oedema is a life-threatening manifestation of acute LV failure secondary to sudden onset of pulmonary venous HT. A sudden rise in LV filling pressure results in rapid movement of plasma fluid through pulmonary capillaries into the interstitial space and alveoli. The patient presents with extreme dyspnea , cyanosis, tachypnea, hyperpnea, restlessness and anxiety with a sense of suffocation. Pallor and diaphoresis are common. The pulse may be thready and the BP may be difficult to obtain. Respirations are laboured and rales are widely dispersed over both lung fields anteriorly and posteriorly. Some patients manifest marked bronchospasm or wheezing (cardiac asthma). Noisy respiratory efforts often render careful auscultation of the heart difficult, but a summation gallop with combination of the atrial and ventricular gallop sound can be heard in diastole. Hypoxemia is severe and cyanosis is deep. CO2 retention is a late, ominous manifestation of secondary hypoventilation.

Right ventricle failure (with or without pulmonary venous HT).

The principal symptoms include fatigue; awareness of fullness in the neck; fullness in the abdomen, with occasional tenderness in the right upper quadrant of the abdomen (over the liver); ankle swelling; and in advanced stages, abdominal swelling due to ascites. Pertinent signs include evidence of systemic venous HT, abnormally large "a" or "v" waves in the external jugular pulse, an enlarged and tender liver, a murmur of tricuspid regurgitation along the left sternal border, right ventricular S3 and S4, and pitting oedema of the lowest parts of the body.

Cyanosis may occur with any form of HF. The cause may be central and reflect hypoxemia. A peripheral component due to capillary stasis with increased A-V O2 difference and resultant marked venous oxyhemoglobin unsaturation may also be present. Improved colour of the nail bed with vigorous massage suggests the presence of peripheral cyanosis. Central cyanosis cannot be altered by increasing local blood flow.

Edema (see water and fluid retention)

9. Laboratory findings

There are no specific **ECG findings** in HF. Abnormalities (e.g. ventricular hypertrophy, acute myocardial infarction or bundle branch block) may provide etiologic clues. The recent onset of rapid atrial fibrillation may precipitate acute RV or LV failure. On the other hand, frequent premature ventricular contractions may be secondary and may be subside when the heart failure is treated.

Chest X-rays: pulmonary venous congestion and increased vascular markings are characteristic of pulmonary oedema. Kerley B lines reflect chronic elevation of left atrial pressure and represent chronic thickening of the intralobular sept from oedema. Venous blood redistribution to the upper lobes is also present. Careful examination of the cardiac silhouette, evaluation of the chamber enlargement and a search for cardiac calcification are important X-ray clues to the etiology of the primary cardiac abnormality.

Echocardiography can evaluate LV as well as other chamber dimensions, ejection fraction and wall motion abnormalities. The degree of LV dilation can also be assessed along with abnormalities of the cardiac valves. The presence of pericardial effusion, intracardiac thrombi, and tumours can also be accurately detected with echo Doppler and color Doppler techniques. The presence and severity of incompetence and stenosis of the aortic, mitral, pulmonic and tricuspid valves can be evaluated. Cardiac calcifications within the cardiac valves as in the mitral annulus and the wall of aorta can be recognized. Underlying artery disease can be indirectly assessed by segmental wall motion abnormalities.

II.3. Pathophysiology of digestive system

II.3.1. Pathophysiology of esophagus

The major symptoms of esophageal disorders are the following: *dysphagia, heart burn, painful swallowing*. Dysphagia is one of the most important symptoms of esophageal disorders. It is either due to a local lesion or is part of a generalized disease.

Patients will complain of something sticking in their throat or chest during swallowing or immediately afterwards.

It is always a serious symptom and cause must be found;

- diseases of the mouth and tongue
- neuromuscular disorders: faryngeal disorders (myastenia gravis), esophageal motility disorders (achalasia, scleroderma, diffuse esophageal spasm, diabetes)
- extrinsic pressure: mediastinal glands, enlarged left atrium, goitre
- intrinsic lesions - foreign body, stricture (benign - corrosive and malign - cancer)
  - low esophageal rings, esophageal webs

Painful conditions of oropharynx: acute tonsilitis, herpangine, which particularly affects the back of the mouth, or oropharynx.

Obstruction: site in the esopnagus: stricture secondary to esophagitis or, more important, to carcinoma. In the case of Paterson-Kelly syndrome are esophageal web forms or obstruction at the upper end of the esophagus.

Mechanical interference with the muscles of deglutition. Extensive infiltration of the tongue (posterior third) or of esophagus wall by carcinoma interferes with the muscular activity of swallowing.

Paralytic conditions: paralysis of thie muscles of swallowing is the feature of acute polyomyelitis affecting the brain.

Neuromuscular incoordination: achalasia

Neurosis; anxiety states, hallucinations, hysterical globe.

Heart bum is a common symptom for acid reflux. The pain can spread to the neck, across the chest and can be difficult to distinguish from the pain of ischaemic heart disease. It occurs at night when the patient lies flat or after bending or stooping. Hot drinks and alcohol often precipitate the pain.

Painful swallowing, without real difficulty is occasionally seen in conditions (immunosupressed patients): herpes simplex and following ingestion of potassium which produce local ulceration if they lodge in the gullet where swallowed lying down and without water.

SIGNS OF THE ESOPHAGEAL DISORDERS

There are a very few signs associated: weight loss as a consequence of dysphagia is the main one.

1. Esophagitis

Esophagitis is an inflammation of the esophagus that has a variety of causes, but so called reflux esophagitis due to hiatus hernia is the most common. Much less often direct microbial invasion, usually by viruses or fungi, is implicated in *immunodeficient* and *debilitated* patients such as those with leukemia and terminal cancer. These are vulnerable to the development of candidal or herpes simplex esophagitis when there are oral infections and gastric intubation has been introduced through the infected teritory.

Reflux esophagitis is an injury to the esophageal wall with subsequent inflammation. It is produced by chronic esophageal reflux, ingestion of corrosive or irritant substances, radiation, prolonged gastric intubation, uremia, graft versus host disease; the main cofactors are heavy smoking and alcohol consumption.

Pathogenesis:

- impairment of the efficacy of the lower esophageal antireflux mechanism that prevents acid peptic secretions from inundating the lower esophagus
- a sliding hiatal hernia significantly predisposes

- increased gastric volume, whatever its basis, contributes to the volume of reflux
- the levels of acid and of pepsin in the gastric secretion determine the injury-producing potential of the refluxate
- inadequate or slowed esophageal clearance of refluxate
- the reparative capacity of the esophageal mucosa is reduced

Any of these influences may assume primacy in individual cases, but more than one is likely to be involved in most instances(fig no 28)

Esophageal ulcers are uncommon complications of reflux esophagitis: hematemesis, or rarely, perforation of esophagus.

Barett's epithelium is defined as a replacement of the squamous epithelium in the lower third of the esopagus by columnar epithelium. It caries a significant risk of malignant transformation to adenocarcinoma.

Infectious esophagitis. *Candidosis* in chronic immunocompromised persons after chemotherapy for malignant diseases, immunosupressive therapy, organ transplant or AIDS; *herpetic esophagitis* associated with lymphomas and leukemias.

Chemical esophagitis results from accidental poisoning in children or attempt to suicide in adults. It is produced by the intake of strong alkaline or acid agents, used in various cleaning solutions.

Esophagitis produced by physical agents are subsequent to external irradiation, nasogastric tubulature.

2. Motor disorders

a. Achalasia, that means "failure to relax", applies to incomplete relaxation of the lower esophageal sphincter (LES) in response to swallowing.

Mechanisms:

- a reduction in number of ganglion cells in the esophageal myenteric plexus
- primary degenerative changes in the vagal branches to the esophagus
- degeneration of the cells of the central vagal nuclei
- decreased neural formation of the inhibitory vasoactive intestinal polypeptide.

Clinical features - dysphagia, sometimes accompanied by retrosternal chest pain and vomiting.

b. **Other motor disorders:**

Congenital atresia and stenosis - atresia implies failure of development of a segment of the esophagus creating discontinuous, blind upper and lower pouches. Stenosis implies marked narrowing of the esophageal lumen and may occur as a developmental defect or may be aquired secondary to chronic esophagitis , neoplastic narrowing, scleroderma or extrinsic compression by mediastinal tumor.

Diverticula - outpouchings of the esophageal wall tend to occur in 3 locations:

- at the pharyngoesophageal junction where defects in the posterior pharyngeal wall create loci of weakness (Zenker's diverticulum)
- near the midpoint of the esophagus where the traheal bifurcation may cause slight narrowing of the esophageal lumen
- immediately above the LES

Rings and webs (the terms are interchangeable; the two categories can be differenciated on the basis of location within the esophagus and the presence or absence of muscularis within constrictions).

The lesions in the lower esophagus are oftenly refered to as **Schatzki's rings.** Upper esophageal more often referred to as webs, are sometimes accompanied by atrophic glositis and iron deficieny anaemia **(Plummer-Vinson or Paterson-Brown-Kelly syndrome).**

Miscellaneous lesions:

Hiatal hernia - a dilated segment of the stomach protrudes above the diaphragm. Two patterns are distinguished:

- sliding hiatal hernia - the esophago-gastric junction is displaced cephalad, resulting in a dilated, bell-shaped segment of the stomach lying above the diaphragm
- paraesophageal (rolling) hiatal hernias - a defect or weaking of the diaphragmatic esophageal hiatus permits a portion of the gastric fundus to balloon into thorax

Lacerations (Mallory-Weiss syndrome) - linear tears in the gastroesophageal wall are uncommon lesions encountered most frequently in chronic alcoholics after a bout of retching or vomiting. They may be located in the terminal esophagus, astride the esophagogastric junction or in the proximate gastric mucosa and are usually not perforating

Varices - when sufficiently and prolonged, portal hypertension induces the formation of by-pass channels between the portal vein and superior vena cava. With prolonged increased pressure, the veins in the lower esophageal plexus and sometimes those in the gastric mucosa of the gastroesophageal junction dilate and eventually become variceal.

3. Esophageal carcinoma

Predisposing influences to esophageal cancer:

- **established (1)** clinical - achalasia, hiatal hernia, reflux esophagitis, Barett's esophagus, Plummer-Vinson syndrome, caustic induced

strictures; **(2)** environmental - alcohol abuse, tobacco use; (3) genetic-tylosis (autosomal condition with 100% risk);

- **questionable** - aflatoxins, nitrosamines, nutritional deficiencies (e.g. vitamins A, C, riboflavin), some trace chemical excess or deficiency (e.g., zinc).

II.3.2. Pathophysiology of gastritis

1. Gastritis

The term gastritis, like indigestion, is used by the public and occasionally by physicians as a catch-all for minor abdominal symptoms such as vague epigastric dyscomfort and mild nausea.In pathologic terms gastritis (G.) can be classified in two types: acute G. and chronic G. (autoimmune and non-autoirmmune).

Types of gastritis and their major associations:

a. acute, induced by NSAIDs, alcohol abuse, low flow states (shock), stress (illness, trauma, emotional problems), cigarette smoking, uremia, toxic substances (acids, alkalis), radiation, helicobacter pylori

b. chronic, induced by aging, Helicobacter pylori, autoantibodies (pernicious anemia), idiopathic, peptic ulcer

c. specific forms; Menetrier's disease, Crohn's disease

a. **Acute (erosive or hemorrhagic) gastritis.** It is a severe G, caused by aspirin or alcohol and is characterized by errosions of gastric mucosa causing hemorrhages of varying severity. Aspirin acts by inhibiting PgE with subsequent platelet aggregation resulting in bleeding. Too much alcohol, followed by aspirin to deal with hangover, can be dangerous because of the combined effect of the two irritations. Diagnostic is established by a combination of endoscopic observations and histological evaluation of biopsy specimens.

Pathogenesis:

- hypersecretion of gastric acid subsequent to neurologic trauma or stress ulcers
- decreased mucus production
- prostglandin deficiency
- reduced turn-over of the gastric epithelial cells
- lowering of the intramural pH of the gastric mucosa

b. **Chronic (non-erosive) gastritis** - is very common and may affect about 10% of the general population. In many cases it causes no symptom. It is a chronic inflammatory disease of the stomach of unknown cause that ranges from mild superficial involvement to severe atrophy of the gastric mucosa; the epithelial

changes may become dysplastic and possibly be transformed into carcinoma. There is no grossly visible mucosal erosion and the cardinal feature is the progressive loss of the capacity to secrete acid (achlorhydria) and as a consequence pernicious anaemia develops.

Classification: type ***A*** - involving the fundus and the body of the stomach - and type ***B***, that is subdivided into "hypersecretory" antral gastritis and "environmental" gastritis (type AB).

Pathogenesis:

Type *A* - autoimmune G - is chararacterized by progressive and irreversible atrophy of both acid - secretory -and pepsine secreting cells; a significant incidence of antibodies to gastric parietal cells.

Atrophic G leads to failure of the secretion of the intrinsic factors and megaloblastic (pernicious) anemia. One of the diagnostic features of pernicious anemia is therefore the total failure of gastric secretion; no acid is secreted even in response to histamin. Antibodies are also formed against thie intrinsic factor. Type B is much more common than type A. It involves only the antrum or being more generalized is likely to be of multifactorial origin, but many aspects accord to *Helicobacter pyllori* (HP) the major role. Colonization of HP in increasing prevalence with age could explain the increased prevalence in elderly (80%). Aging and HP are providing "a substrate" on which other pathogenic influences may get, such as chronic alcohol abuse, cigarette smoking, reflux of billiary secretion into the stomach and the chronic use of NSAID. The loss of parietal cells and their production of intrinsic factor blocks the absorption of vitamin B12 so inducing pernicious anemia.

Most important is the relationship of chronic G to the development of peptic ulcers and gastric carcinoma. Most patients with peptic ulcers, whether duodenal or gastric, have gastritis that persists after the ulcers heals , suggesting that the gastritis is primary.

Type AB (so-called environmental gastritis) is multifactorial, aging and HP being the most important causes.

c. Specific forms of gastritis:

- **Menetrier's disease (giant hypertrophic gastritis)** is an uncommon gastric disorder with giant hypertrophy of the mucosal folds of the grater curvature, fundus and body of the stomach. It is considered to be a precancerous condition
- **Idiopathic granulomatous gastritis** is defined as the presence of epitheloid granulomas in the gastric mucosa when specific granulomatous disorders are excluded.

- **Eosinophilic gastritis** is a rare disease in which eosinophilic inflammation involves all layers of the stomach wall or is selectively localized in a single layer, mainly affecting the antrum and pylorus.
- **Miscellaneous causes of gastritis** include radiation, Crohn's disease and sarcoidosis, specific infections such as tuberculosis, syphillis and a variety of fungi.

2. Pyloric stenosis appears in two settings:

- in infants, within the first month of life, with familial predisposition and incidence in males three to four times superior to females.
- in adults, rarely, possibly secondary to local diseases such as: pyloric ulcer, prolonged pyloric spasm or underlying pyloric carcinoma but sometimes of any antecedent condition

There is marked muscular hypertrophy of the pylorus and thickening of the wall creating a sausage-shaped mass, mucosal oedema with submucosal lyimphocytic infiltration further narrowing the pyloric canal

3.3. Pathophysiology of Peptic ulcer

Definition:: peptic ulcer disease (P.U.C.) refers to breaks in the mucosa of the stomach and small intestine, principally the proximal duodenum that are produced by the action of gastric secretion. It affects most frequently the distal stomach and proximal duodenum. The triggering factor for developing peptic ulcer is the gastric secretion of hydrochloric acid; a person who does not secrete acid will not develop a peptic ulcer.

Epidemiologic considerations. It afflicts about 10% of general population; persons between 30-60 are the most affected. The sex distribution for duodenal peptic ulcer displays main predominance; the incidenge of gastric peptic ulcer is the same for men and women.

Normally, **gastric secretion,** is the result of 4 major cell types of gastric mucosa glands:

- *The gastrin producing cells (G cells)* are found in the antrum; with stimulation, they release gastrin into the blood stream
- *Mucous producing cells* are located through the stomach; their function is to produce lubricating mucus
- *Parietal cells* found in the stomach body and fundus secreted hydrochloric acid and intrinsic factor
- *The chief cell* is also found in the body and fundus of the stomach. It produces pepsinogen which is cleaved by acid to pepsin; a proteolytic

enzyme secretion from chief cells is stimulated by proteins and also by factors that stimulate hydrochloric secretion.

The 3 known in vivo agonists of hydrocloric secretion are: acethylcholine, gastrin and hystamin (only type II receptors are found in the stomach). These three agonists seem to work through a final common pathway to cause hydrochloric secretion: the maximum hydrochloric secretion by the parietal cell can be accomplished by maximum stimulation of acetylcholin release, maximum histamin receptor stimulation or infusion of large amounts of gastrin. Blockage of anyone of these three agonists will decrease hydrocloric secretion, even if maximum stimulation by one of the other agonists is maintained.

Defensive forces:

Several factors act to protect the gastric mucosa from autodigestion collectively referred as "the mucosal barrier".

- **Mucus secretion.** Surface and mucous neck cells in the stomach and duodenum (as well as duodenal Brunerr's glands) secrete a thin layer of mucus, which consists of a water-insoluble, viscoelastic gel, with a diffusion coefficient for H+ that is one fourth that of water. This gel is also impermeable to large molecules such as pepsin. Its production is stimulated by luminal acid and vagal stimulation and its release from mucous cells is increased by prostaglandins.
- **Bicarbonate secretion.** Both the stomach and the duodenum secrete bicarbonate into the boundary zone of adherent mucus, creating a relatively alkaline microenvironment immediately adjacent to the cell surface. Gastric bicarbonate secretion is about 5 to 10% of maximal acid secretion and is stimulated by luminal acid, mild irritants, vagal stimulation and prostaglandins. Carbonic anhydrase is present not only in surface foveolar cells but also in parietal cells themselves, perhaps contributing to local protection at the apical cell surface of parietal cells.
- **Epithelial barrier.** Mucosal epithelial cells are bound to each other by intercellular tight junctions, providing a barrier to the back-diffusion of hydrogen ions. When the epitehelium is disrupted, repair occurs rapidly by the process of restitution, in which existing cells migrate along the exposed basement membrane to fill in the defects created by the sloughing of cells. Gastric epithelial cells also can replicate rapidly in response to injury.
- **Mucosal blood flow.** The gastric mucosa has a rich blood supply consisting of extensively arborizing capillaries. A righ blood flow is necessary to provide oxygen, bicarbonate, and nutrients to epithelial cells and to remove back-diffused acid. Mucosal blood flow is regulated by local vasoactive mediators, particularly endogenous nitric oxide, prostaglandins, and neuropeptides; increased blood flow occurs simultaneously with stimulation of acid secretion. Just as adequate blood flow is critical to mucosal function, mucosal ischemia may play a key role in promoting mucosal injury. Blood flow may by adversely affected by severe medical or surgical stress, exogenous agents, such as aspirin and alcohol, and entry into the lamina propria of luminal agents, such as acid and pepsin.

- **Prostaglandin protection.** No topic is more controversial than the role of prostaglandins in mucosal function. Exogenous prostaglandins visibly protect the gastric mucosa from experimental alcohol-induced injury, but microscopic damage to surface epithelial cells is still extensive. Although several mechanisms may be operative, such as enhanced mucus secretion and bicarbonate output, the physiologic role of prostaglandin protection remains to be established.
- **Neural and muscular components.** Afferent neurons within the mucosa of the stomach and per has the duodenum can trigger a protective reflex vasodilatation when toxins or acid breach the epithelial barrier. In addition, the muscularis mucosa may serve to limit injury. Superficial damage, limited to the mucosa, can heal within hours to days. When damage extend into the submucosa, a mini mum of several weeks is required for complete healing.

The duodenum may also be excessively acidified by the rapid emptying of gastric contents. Accelerated gastric emptying has been noted in patients with duodenal ulcers although, as with other factors, there is substantial overlap with normal rates. Normally acidification of the duodenal bulb inhibits further gastric emptying. It has been reported that in the majority of patients with duodenal ulcer this feedback inhibitory mechanism is absent, and duodenal acidification results in continued, rather than delayed, gastric emptying. Evidence suggests that rapid gastric emptying may in some cases be an inherited abnormality.

The pH of the duodenal bulb reflects the balance between the delivery of gastric juice and its neutralization by biliary, pancreatic, and duodenal secretion. The production of duodenal ulcers requires an acidic pH in the bulb - that is, an excess of acid over neutralizing secretions. In ulcer patients the duodenal pH following a meal falls to a lower level and remains depressed for a longer time than in normal individuals. This duodenal hyperacidity certainly reflects the gastric factors discussed above. The role of neutralizing factors, particularly secretin-stimulated bicarbonate

secretion by the pancreas and production of bicarbonate by the duodenal mucosa, is uncertain, and the subject remains controversial.

The role of impaired mucosal defenses against peptic ulceration is not well delineated. The mucosal factors, including the function of prostaglandins, may or may not be similar to those protecting the gastric mucosa.

Although gastric juice is clearly implicated in the production of duodenal ulcers, its role in the formation of gastric ulcers is more difficult to asses. A number of patients with gastric ulcers display hypersecretion of acid, but most secrete not only less gastric acid than patients with duodenal ulcer, but even less than normal people. The genesis of gastric hypersecretion is obscure. The factors implicated include back-diffusion of acid into the mucosa, decreased parietal cell mass, and abnormalities of the parietal cells themselves. Gastric ulcers in patients with acid hypersecretion are usually near the pylorus and are considered variants of duodenal ulceration. Interestingly, the intense gastric hypersecretion seen in the Zollinger-Ellison syndrome is associated with severe ulceration of the duodenum and even the jejunum, but rarely with gastric ulcers.

The occurrence of gastric ulcers in the face of gastric hyposecretion implies the following possibilities: that the gastric mucosa is in some way particularly sensitive to low concentration of acid; that some material other than acid damages the mucosa; or that the gastric mucosa is exposed to potentially injurious agents for an unusually long period of time. As discussed in the section entitled Erosive Gastritis, the mucosal barrier to the action of acid, and perhaps to other contents of the stomach, may be impaired in some patients with gastric ulcers, although the evidence is far from conclusive. Although nonerosive, superficial, and atrophic gastritis often accompany gastric ulcers, it is not known whether the ulcer or the gastritis is the primary event.

There is considerable interest in the possibility that peptic ulcer disease may be caused, at least in part, by colonization of the upper gastrointestinal tract by *Campylobacter pylori*. However, the evidence is contradictory, and a role for this organism in the pathogenesis of peptic ulcers remains controversial.

In summary, the pathogenesis of gastric and duodenal peptic ulcers remains poorly understood. The only certainty is that at least some acid is required for both. The contribution of the mechanisms discussed above are, for the most part, hypothetical, and their roles relative roles remain to be defined.

II. Aggressive forces

- *Acid secretion* but only 1/3 of patients with duodenal ulcer secrete excessive acid and hyperacidity is not a feature of gastric ulcer. "No acid, no ulcer".
- *Peptic activity* derived from pepsinogen is critical to ulcer production, but hypersecretion is not requisite.

- *Helicobacter pylori infections* of the gastric antrum is generally viewed as important, but there are doubters.
- *NSAIDs* may be ulcerogenic. Aspirine is the most offender, but a variety of other NSAIDs has also been implicated.

Imbalance in the defensive and aggressive forces underlines the genesis of peptic ulcer.

GASTRIC ULCER

Gastric ulcer (GU) is more commonly seen in people from 40- 60 years.

Hydrochloride acid hypersecretion is not a primary factor since most of these older patients have normal or even less than normal rate of maximum stimulation of HCl secretion.

The possible mechanisms of mucosal injuries and increase permeability to H^+ include four mechanisms:

- reflux of bile salts and lysolecithin into the stomach from the duodenum (pilor incompetence) can cause direct damage to cell membrane.
- ingestion of aspirin conducts to decreased cyclooxygenase levels resulting in decreased prostaglandin secretion with decreased mucus secretion and impairment of tile protective mechanisms, very thin mucuos barrier. Both aspirin and alcohol ingestion can cause a change in the potential defense across the cell membrane, allowing H+ back diffusion to occur and cause cellular damage.
- stress can lead to gastric erosions (acute erosive gastritis) that can go on to form ulceration.
- gastric outlet obstruction may keep gastric mucosa bathed into acid.

The mucosal defensive barrier may be defective in patients who develop GU. As a result., the back diffusion of H+ can cause:

- pepsin activation, and therefore protein digestion.
- histamin release with further stimulation for H+ production.

Mucous protection or secretion of a protective mucus by die parietal cells may be impaired. This appears to be a very thin, mucous barrier, probably containing bicarbonate gradient (regulated by Pg): that is an important, first line defensive against H^+.

If epithelial renewed is slowed from its normal 4- to 6-days turnover time to a longer time. 'he regencration capacity of the stomach wilt be impaired. This may be important in patients who are malnutrished. Given the preceeding discussions, it is not surprising that GU are common in patients with gastric outlet obstruction due to piloric channel or duodenal bulb disease, in patients tanking aspirin or alcohol on a

regular basis, in patients suffering from intense stress (psychic or neurosurgical stress, burns or septicemia) and in those patients with chronic disease such as rheumatoid arthritis, chronic lung disease, renal failure. Hemorrhages occur when the ulcerations extends through a blood vessel, and can be massive when an artery of some size is disrupted.

Penetration of GU into an adjacent structure may also cause symptoms: penetration into the pancreas results into pancreatitis and pain.

Perforation will release air and gastric juice into the abdominal cavity resulting in signs of peritonitis and free air under the diaphragm.

DUODENAL ULCER

Duodenal ulcer (DU) is more common than GU but it is inappropriate to draw any final firm conclusion regarding trends in the incidence of DU disease.

Pathogenesis particularities

Genetic factors. DU disease illustrates the importance of genetic factors and their interaction with the environmental mechanisms.

First degree relatives of patients with DU have a 3-fold increased risk of developing DU but do not have a similar increase of risk of developing a GU.

Studies of blood groups antigen show that the risk of DU is about 30% higher in persons with type 0 blood than in A, B and AB individuals.

The quarter of population that does not secrete blood group antigen in the saliva and gastric juice is at *50%* increased risk of developing a DU; the risk is greatly increased when non-secretory status is combined with blood group.

II.3.4. Pathophysiology of pancreatitis

DEFINITION

Pancreatitis is defined as an inflammatory condition of the exocrine pancreas that results from injury to acinar cells. Depending on its severity and duration, pancreatitis presents in a variety of clinical forms. These range from a mild, self-limited disease, consisting of acute inflammation and edema of the stroma with little or no acinar cell necrosis, to the more severe and sometimes fatal acute hemorrhagic pancreatitis with massive necrosis.

ACUTE PANCREATITIS

Acute hemorrhagic pancreatitis is a condition of middle age, with a peak incidence at 60 years. It is often associated with chronic biliary disease and alcohol abuse and erupts abruptly, usually following a heavy meal or excessive alcohol intake. It is more common in men than in women, especially when it is associated

with the chronic abuse of alcohol. Clinically, the patient presents with severe epigastric pain that is referred to the upper back and is accompanied by nausea and vomiting. Within a matter of hours catastrophic peripheral vascular collapse and shock ensue. When shock is sustained and profound, pancreatitis may be complicated within the first week of onset by the adult respiratory distress syndrome and acute renal failure, a situation that is fatal in 7% of cases. Early in the disease, pancreatic digestive enzyme is released from injured acinar cells into the blood and the abdominal cavity. Elevation of serum amylase and lipase levels as early as 24 to 72 hours is diagnostic, as are high enzyme levels in the abdominal ascitic fluid.

The most prominent tissue alteration in acute pancreatitis is acinar cell necrosis, an intense acute inflammatory reaction, and foci of necrotic cells.

ETIOPATHOGENESIS OF ACUTE PANCREATITIS

Autopsy studies at the turn of the century established the association of the chronic cholecistitis and cholelithiasis with acute hemorrhagic pancreatitis. In some cases gallstones were found lodged near the orifice of the common duct beyond the point where the pancreatic duct joins it. Sine a stone impacted at this site obstructs both ducts; it would be expected to cause the reflux of bile into the pancreas. Therefore, it was theorized that such obstruction was the etiologic factor in the development of acute hemorrhagic pancreatitis. This notion was prevalent for many years and gained support from experimental studies in animals in which hemorrhagic pancreatitis was induced by retrograde infusion of a mixture of pancreatic juice and bile into the main pancreatic duct. However, in recent years it has become increasingly apparent that although pancreatitis is often accompanied by conditions that serve to impair normal duct secretion, frank obstruction of the common duct or pancreatic duct is often not present. Increasingly, studies suggest that failure of one or more of the complex systems of physiological checks and balances that serve to prevent the inappropriate activation of pancreatic enzymes and to protect the host from their deleterious effect may also contribute to the development of acute pancreatitis. Although the mechanisms that initiate the various forms of pancreatitis have been the focus of much study and research, they continue to elude us and are the subjects of speculation. From the foregoing consideration of the various types of pancreatitis, **it is clear that a breakdown of intracellular compartimentation of digestive proenzymes synthesized by the acinar cell and inappropriate and premature activation of these proenzymes are common to all variants of pancreatitis. The ultimate pathogenetic process in acute pancreatitis is proteolysis, lipolysis, and hemorrhage resulting from the destructive effect of pancreatic enzymes released from acinar cells.** Differences in the severity and duration of membrane damage may in part determine the type of pancreatitis that ultimately develops.

What remains to be clarified is how pancreatic enzymes are activated and released within the pancreas. Proposal about possible mechanisms of pancreatic injury, based on animal studies, is as follows:

1. Duct obstruction.

Since the main pancreatic duct joins the common bile duct in two-thirds of normal individuals, gallstones impacted in the ampula of Vater can, presumably, cause pancreatic obstruction. Continued pancreatic secretion increased ductal pressure, which is thought to lead to rupture of small pancreatic ductules, extravasation of pancreatic secretions into the interstitium, digestive enzyme activation, and subsequent pancreatitis. How the enzymes become activated remains unclear. Reflux of bile *per se* is not felt to play a role.

The pancreas is protected from the harmful effects of its lytic enzymes by a series of highly compartimented systems of intracellular membranes. These membranes effectively isolate the pancreatic enzymes from their synthesis by the rough-surfaced endoplasmic reticulum to their release into the ductular lumen in response to stimulation by the gastrointestinal hormone cholecystokinin. This process involves the extrusion of the nascent proenzymes into the cisternae of the endoplasmic reticulum, from which they are moved progressively by a system of vesicles to the *cis* and *trans* elements of the Golgi complex, and from that site to condensing vacuoles, from which the zymogen granules are ultimately derived. On secretion the membrane of the granule fuses with the plasma membrane before its extrusion by exocytosis. At each step of their formation and secretion the enzymes are totally sequestered in a membrane-bound space. The various potent inhibitors of proteolytic enzymes present in many body fluids and tissues constitute a second line of protection, defending the organism against inappropriate activation of the digestive proenzymes of the pancreas. However, this defense is not total. Four potent protease inhibitors have been identified in human plasma: α1-antitripsin, α2-macroglobulin, C1 esterase inhibitor, and pancreatic secretory trypsin inhibitor. Although collectively these can inhibit two types of trypsin in addition to chymotrypsin and elastase, they are without effect on two other potent proteases, carboxypeptidases A and B. These inhibitors bind strongly to the proteases and render them inactive. Although α2-macroglobulin reduces the capacity of either of the trypsin molecules to digest protein, it does not completely prevent them from cleaving small synthetic peptides. Thus, trypsin activity is demonstrable in plasma, even when the inhibitor binds trypsin. Further, a tyrosine inhibitor in human pancreatic juice is unable to inhibit the enzyme completely, even when the inhibitor is present in excess. Apparently the inhibitor is digested by the trypsin to which is bound, a reaction that requires calcium ions. Thus, despite the variety of inhibitors of trypsin in different body compartments, the protection they render is less than complete. Since it turns out that activated

trypsin is also able to activate other pancreatic enzymes, such as chymotrypsinogen, proclastases, phospholipase, and procarboxypeptidase, its incomplete inhibition in pancreatic juice and plasma poses a hazard.

Secretion by acinar cells delivers fluid rich in proenzymes to the ductules, where they are activated almost immediately. Although most of the secretion is discharged into the duct system and enters the duodenum, a small amount diffuses back into the periductular extracellular fluid and eventually the plasma. This happens because normal ducts contain fluid under some, albeit low, pressure. Thus, any condition that tends to diminish the patience of pancreatic ducts, which or the easy outflow of exocrine secretion could be expected to exacerbate back-diffusion across the ducts, which can trigger a massive inappropriate activation of digestive proenzymes. If the obstruction is sufficiently severe, this process could even involve the acinar cells. The transudation of pancreatic secretion into periductal pancreatic tissues and eventually peripancreatic tissue leads to chemical injury. The activated enzymes digest proteins, lipids, and carbohydrates of cell membranes, and when mixed with bile converts lecithin to the potent cytotoxin lysolecithin. Damage to the capillaries leads to hemorrhage and local anoxia, which further intensifies and extends tissue damage.

Well-documented causes of pancreatic duct obstruction include gallstones, frequently in association with chronic cholecystitis, and chronic alcohol abuse. Although ethanol is well recognized as a chemical toxin, a direct toxic effect on pancreatic acinar or duct cells has yet to be demonstrated. However, ethanol can adversely affect the pancreas by causing spasm or acute edema of the sphincter of Oddi, especially following an alcoholic binge, and by stimulating the secretion from the pancreas to secrete pancreatic juice. When these effects occur together (i.e., enhanced secretion into an obstructed duct), the results may be disastrous. The most cases of alcohol pancreatits now appera to be acute exacrebations of chronic pancreatitis, rather than acute pancreatitis *per se*.

Tabel 18 - Conditions and etiologic agents associated with pancreatitis

Cholelithiasis
Alcoholism
Idiopathic
Other causes
Abdominal operations
Endoscopic procedures wwith injection into pancreatic duct
Infection: bacteria, viral , and parasitic
Ischemia or vasculitis
Drugs
Trauma
Extension from adjacent inflamed tissues
Mass lesions
Endocrine/metabolic: hereditary, hyperlipidemias, hypercalcemia, hemochromatosis, uremia, diabetic ketoacidosis, hypothermia

2. Acinar cell injury

This is an early event in the evolution of many forms of acute pancreatitis. Alcohol, in particular, may be directly toxic to acinar cells, leading to severe intercellular leak of digestive enzymes. In addition, other factors that cause pancreatic acinar cell injury and pancreatitis include viruses, endotoxemia, ischemia, drugs, trauma, hyertriglyceridemia, and hypercalcemia. The mechanism by which some of these induce injury are known, but those for others – such as corticosteroids, estrogens, azathioprine, hyperglyceridemia and hypercalcemia – remain unclear. In hypertriglyceridemia and hypercalcemia, it is thought that toxic fatty acids are formed by the action of trypsinogen by high levels of triglycerides induces edema, hemorrhage, and a striking release of free fatty acids into the perfusate.

3. Deranged intracellular transport of pancreatic enzymes

This is a more subtle alteration, in which apical secretion is inhibited in alcohol-induced pancreatitis. Instead, these enzymes are missorted to a vacuole containing lysosomal enzymes, leading to enzyme activation and rupture of these organelles.

CHRONIC PANCREATITIS

Chronic pancreatitis is thought to result from recurent bouts of acute pancreatitis, which lead to a progressive destruction of acinar cells, followed by healing and fibrosis. As a result, exocrine and endocrine functions are lost.

Etiopathogenesis of chronic pancreatitis

Like acute pancreatitis, chronic pancreatitis is associated with alcoholism and, less commonly, with biliary tract disease, hypercalcemia, or hyperlipidemia. About one half of cases are seen in patients without any of these risk factors. The most common type of chronic pancreatitis is chronic calcifying pancreatitis, a disorder most frequently associated with alcoholism. Intraductal protein plugs eventually calcify and lead to the formation of stones in the ducts. In chronic pancreatitis following sustained alcohol abuse, ductules and ducts are so often filled with thick proteinaceous secretion that some have concluded that such secretions may be an important mechanism of obstruction. Since alcohol is a potent secretagogue for the exocrine pancreas, one can visualize a situation of secretion against obstruction. In another form of this disease, chronic obstructive pancreatitis, stenosis of the sphincter of Oddi is associated with gallbladder stones. Although in this condition the pancreatic ducts are filled with thick proteinaceous secretions, they are rarely the focus of calcification or stone formation.

Chronic pancreatitis is more common in men. Diabetes mellitus, pancreatic insufficiency with its attendant steatorrhea and malabsorbtion, and pancreatic pseudocysts are frequent complications in the late stages of chronic pancreatitis.

II.3.6. Malabsorptiom syndromes

Normal digestion and absorption of food involves two phases:

I. *An intraluminal phase* in which proteins and fats are broken down into assimilable forms and fats are solubilized by bile salts.

II. *An intestinal phase* which involves the further hydrolysis of carbohydrates by disaccharidases in the brush border of the small intestine and the mucosal cell uptake and transport of hydrolysed products derived from food as well as formation of chylomicrons from trygliceride and cholesterol.

Transport across the epithelial cells to lymphatics or blood vessels is the final stage in the normal handling of food stuffs.

Malabsorption (MA) is a general term used to describe a number of clinical conditions in which one or more important nutrients are inadequately absorbed by the gastrointestinal tract.

Major forms of MA

I. The intraluminal phase is deranged by:

- Interruption of the normal continuity of the distal stomach and duodenum occurs after gastro-duodenal surgery (gastrectomy, antrectomy, pyloroplasty)
- Pancreatic dysfunction - pancreatitis, cystic fibrosis, carcinoma.
- Deficient or ineffective bile salts which may result from impaired excretion of bile (liver disease with inadequate delivery of bile to the duodenum or dysruption of the intrahepatic circulation by billiary tract destruction or colestatic liver disease), bacterial overgrowth (seen in conditions such as multiple diverticula of the small bowel, blind loop syndrome, muscular or neurogenic defects of the intestinal wall e.g. amiloidosis, scleroderma, diabetic enteropathy) - bile salts are deconjugated by the excess of small bowel bacteria - and absence or by-pass of the distal illeum (surgical excision or anastomoses, fistulas, ileal disease e.g. Crohn's disease, lymphoma).
- Abnormally low intraduodenal pH is seen in patients with hypersecretion secondary to gastrinoma (Zollinger- Ellison syndrome results in inactivation of the panncreatic enzymes by excess gastric acid).

II. The intestinal phase of absorbtion may be interrupted at four different points:

- **microvili** - abnormal function of the microvili may be primary (as in primary disaccharidase defficiencies) or secondary when there is damage to the vili is in celiac disease (sprue).

- **absorption area.** The presence of vili and microvili creates an additional absorbtive area that is equivalent to a basket-ball court. It may be diminished by small bowel resection (short bowel syndrome), gastrocolic fistulas (by-passing the small intestine or diseases associated with mucosal damage (celiac disease, tropical sprue, Whipple's disease)
- **metabolic function of absorptive cells.** Nutrients within the absorptive cells depend for their transport to the circulation on their metabolism within these cells. Non-specific damage to small intestinal epithelial cells occurs in celiac disease, sprue tropical, Whipple's disease and gastrinoma. Specific metabolic dysfunction is seen in a-beta lipoproteinemia.
- **transport.** Nutrients are transported from the intestinal epithelium through the intestinal wall by the way of blood capillaries and lymphatic vessels. Impaired transport of nutrients through these conduits is probably an important factor associated with Whipple's disease, intestinal lymphoma and congenital lymphangiectasia.

Although abnormalities in anyone of the four components of the intestinal phase may cause MA, some diseases affect more than one of these components.

Clinical features

MA may be either *specific or isolated,* involving a single nutrient, or generalized, *pan-malabsorption* -MA of several or all major nutrients.

Generalized MA leads to generalized malnutrition manifested by weight loss and sometimes cachexia; in children it is expressed as "failure to thrive[11].

Specific deficiency states may be manifested by anemia secondary to a deficiency of iron, folic acid or vitamin B 12; patients may feature bleeding diatheses (vitamin K deficiency), tetany, osteomalacia (vitamin D and calcium MA), glositis, keilosis, dermatitis and peripheral neuropathy (vitamin B group deficiency).

Laboratory evaluation

Thev may only detect specific forms of MA. Quantitative fecal fat analysis, D-xylose absorption, 14-C02-cholyl-glycine breath test, lactose tolerance test, Shilling test are the most used in practice.

CELIAC DISEASE (CELIAC SPRUC) (CD)

It is characterized by generalized malabsorption; a typical but non-specific small intestinal mucosal lesion; a prompt clinical and slower histologic response to withdrawal of gluten-containing foods from the diet. Clinically, celiac disease is characterized by generalized MA. The hallmark of CD is a flat small intestinal

mucosa with blunting or total disappearance of viii. abnormal epithelial cells on the mucosal surface and increased cellularity of the lamina propria but not of the deeper layers.

WHIPPLE'S DISEASE (WD)

It is a rare systemic disorder in which the small intestine is consistently involved and MA is the most proeminent feature. It most commonly affects white men in their 30s - 40s. Other clinical findings include fever, increased skin pigmentation, anemia, lymphadenopathy, arthritis, pericarditis, pleurisy, endocarditis and central nervous system involvement. WD typically shows infiltration of the small bowel mucosa by large macrophages that are packed with small, rod-shaped bacili.

ABETALIPOPROTELILEIILIA

It is an autosomal recessive inherited disease characterized by a failure to synthesize apoprotein B, a constituent of the membrane coat of low density lipoproteins. It is an example of MA resulting from a metabolic defect with the small intestinal absorptive cells dial lack apoprotein B and fail to assemble chylomicrons. The other manifestations of the disease result from defects in cell membrane structure manifested in erythrocytes as acanthocytosis and central nervous system as selective demyelinisation of the posterior columns.

HYPOGAMMAGLOBULINEMIA

MA occurs frequently in patients with hypogammaglobulinemia. The histologic appearance of the small intestine may be normal or nodular lymphoid hyperplasia may be seen. Most patients with MA arc found to be infected in the small intestine with Giardia lamblia.

CONGENITAL LYMPHANGIECTASIA

It probably reflects a generalized malformation of the lymphatic system; it is an impaired transport of chylomicrons resulting in steatorea. These patients suffer from protein-loosing entheropathy, condition characterized by excessive loss of plasma protein into the gut.

TROPICAL SPINE

It is characterized by progressively severe malabsorption and nutrient deficiency. Typically, stetorrhea, anemia and weight loss are followed by progressively severe manifestations of folic acid and vitamin B 12 deficiencies and hypoalbuminemia.

RADIATION ENTERITIS

Abdominal enteritis may cause transient damage to the small intestinal mucosa. Anorexia, abdominal cramps and changes in bowel habits occur frequently tile course of abdominal radiation therapy and laboratory studies ill such patients indicate MA of bile salts mid disaccharides.

Table 19 - Agents that alter basal LES pressure

Increase Pressure	Decrease Pressure
Autonomic agents	
Cholinergic (muscarinic) agents (bethanechol) Alpha-adrenergic agonists (phenylephrine, norepinephrine) Anticholinesterase (edrophonium)	Cholinergic (nicotinic) agent (nicotine) Beta-adrenergic agonists (epinephrine, isoproterenol) Alpha-adrenergic antagonists (pheri-tolamine) Anticholinergics (atropine) Dopamine
Hormones	
Gastrin and pentagastnn Motilin Bombesin Prostaglandin F_2	Secretin Cholecystokinin Glucagon GIP and VIP Prostaglandins E_1, E_2, A_2 Progesterone and estrogen
Others	
Histamine (through H1 receptor) Gastric alkalinization Metoclopramide Protein meal	Histamine (through H2 receptor) Nitrites and nitrates Caffeine Fatty meal Theophylline Chocolate Ethanol (high dose) Sedatives Peppermint

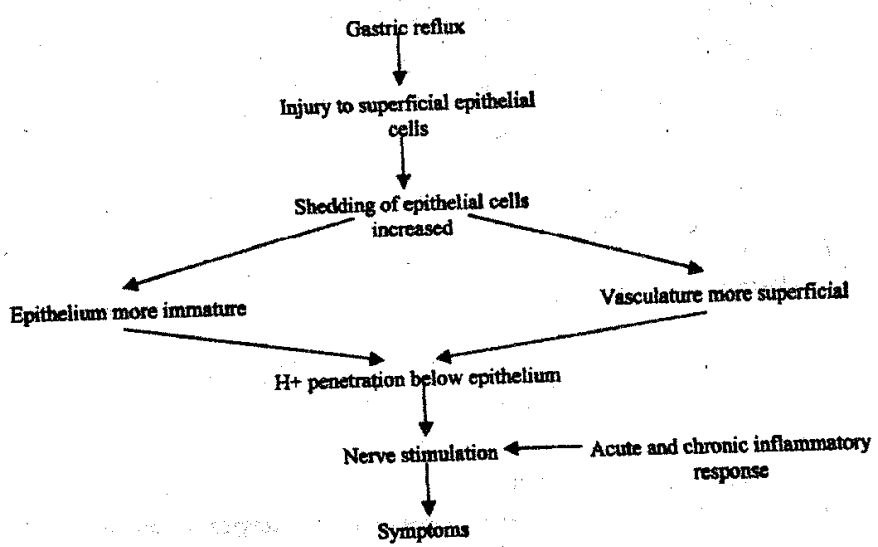


Figure no. 28

Possible mechanism for symptoms in reflux esofihagitis.

MALABSORPTION SYNDROMES

1. Impaired digestive function
   a. Pancreatic diseases or resection
   b. Reduced bile salts
      (I) Parenchymal liver disease
      (2) Cholestasis
      (3) Bacterial destruction of bile salts
      (4) Drugs which bind or precipitate bile salts
   c. Postgastrectomy
2. Intestinal infections
   a. Tropical sprue
   b. Whipple's disease
   c. Blind loop syndrome
   d. Chronic giardiasis
   e. AIDS (various infections)
3. Reduced absorptive area

a. Ileal resection

4. Defective mucosal absorption
   a. Lymphatic obstruction
   b. Congestive cardiac failure
   c. Celiac disease
   d. Crohn's disease
   e. Tropical sprue
   f. Disaecharidase deficiency
   g. Radiation damage
   h. Amyloidosis
   i. Systemic sclerosis
5. Unknown mechanisms
   a. AIDS enteropathy

EFFECTS OF MALABSORPTION

1. Diarrhea and steatorrhea (fatty diarrhea) caused by in-creased fecal fat and water-Serum cholesterol is decreased secondarily.
2. Weight loss, muscle wasting and fatigue caused by in-creased nitrogen and fat excretion and impaired glucose absorption
3. Stunting of growth in children caused by protein deficiency
4. Anemia resulting from impaired iron, vitamin B_{12} or folate absorption
5. Calcium loss leading to paresthesias and tetany, and osteomalacia or osteoporosis
6. Malabsorption of fats leading to failure of absorption of vitamin K and bleeding tendencies caused by reduced prothrombin formation
7. Failure of absorption of other fat-soluble vitamins, *A*, D and E
8. Edema resulting from protein loss and hypoalbuminemia
9. Stomatitis or glossitis resulting from deficiencies of B group vitamins

II.3.6. Pathophysiology of liver disease

A. STRUCTURE RELATED TO PATHOLOGY

1. The hepatocyte and its polarization

A hepatocyte has two functional surfaces: the **apical surface** forms the bile canaliculus, while the **basolateral surface** is in contact with the blood stream via the sinusoids. Very different activities go forward at these regions of the hepatocyte plasma membrane: processes related to bile transport and secretion act at the apical

plasma membrane, whereas uptake from and secretion into the bloodstream are processes that occur across the basolateral membrane.

It is because of cell polarization that hepatocyte disfunction can sometimes involve disruption of the bile flow (cholestasis) with relative preservation of the other functions. There is, however, no clear line between the consequences of disturbed apical and basolateral functions: Cholestasis, while initially a disorder of the apical bile flow, is ultimately manifested at the basolateral surface. This is because it is at the basolateral surface that bilirubin and other substances to be excreted across the apical plasma membrane into the bile must first be taken up from the bloodstream. Similarly, disruption of energy metabolism or protein synthesis, while initially impinging on the secretory and metabolic processes of the hepatocyte, will ultimately affect the bile transport machinery in the apical plasma membrane as well.

2. Concepts of liver organization

Lobules: Liver architecture has been traditionally described in terms of the lobule. Neat arrays of hepatocyte plates are organized around individual central veins to form hexagons with **portal triads** or **spaces** (sheath-like structures containing a portal venule, hepatic arteriole, and bile canaliculus) at their corners. The hepatocytes adjacent to the portal triad are termed *the limiting plate*. Disruption of the limiting plate is a significant diagnostic of some forms of immune-mediated liver disease, as may be seen, for example, at liver biopsy in a patient with liver disease of unknown cause.

Functional zonation refers to a physiologically way to think liver architecture in the terms of the portal-to-central blood flow: Blood entering the sinusoids from a terminal portal venule or hepatic arteriole flows past hepatocytes closest to those vessels first (termed **zone 1 hepatocytes**) and then percolates past **zone 2 hepatocytes** (so called because they are not the first hepatocytes reached by blood entering the hepatic parenchyma). The last hepatocytes reached by blood before it enters the central vein are the **zone 3 hepatocytes.**

*Thus, a **liver acinus** is defined as the unit of liver tissue centered around the portal venule and hepatic arteriole whose hepatocytes can be imagined to form concentric rings of cells in the order in which they come into contact with portal blood, first to last.*

- Hepatocytes at either extreme of the acinus (zones 1 and 3) appear to differ in both enzymatic and physiologic functions:
- **Zone 1 hepatocytes**, exposed to the highest oxygen concentrations, are particularly active in gluconeogenesis and oxidative energy metabolism. They are also the major site of urea synthesis (since freely difusible

substances such as ammonia absorbed from protein breakdown in the gut will be largely extracted in zone 1).

- Conversely, **zone 3 hepatocytes** are more active in glycolysis and lipogenesis (processes requiring less oxygen).

The fact that hepatocytes in the different zones of the acinus see blood in particular sequence has a great pathophysiologic significance. Since zone 1 hepatocytes see blood that just has left the portal venule or hepatic arteriole, they have access to the highest concentrations of various substances - both good (oxygen, nutrients) and bad (e.g. drugs and toxins absorbed from the gastrointestinal tract). Zone 2 hepatocytes receive blood containing less of these substances, and zone 3 hepatocytes are bathed in blood largely depleted of them. However, zone 3 hepatocytes see the highest concentrations of products (e.g. drug metabolites) released into the bloodstream by the hepatocytes of zones 1 and 2. *Thus, direct poisons have their most severe impact on zone 1 hepatocytes, while poisons that are generated as a result of hepatic metabolism will cause more damage to those of zone 3. Similarly, since sinusoidal blood around zone 3 has the lowest oxygen concentration, hepatocytes of this zone are at greatest risk of injury under conditions of hypoxia.*

3. Capacity for regeneration

While the normal liver harbors very few cells in mitosis, when hepatocytes are lost, poorly understood mechanisms stimulate proliferation of the remaining hepatocytes. This is why in most cases of fulminant hepatitis with massive hepatocellular death, if the patient survives the acute period of hepatic disfunction, recovery will be complete. Hepatocyte regeneration, however, may be a two-edged sword. Under certain circumstances, the consequence of regeneration is not the restoration of the normal liver but rather augmentation of hepatocyte mass with loss of normal liver architecture. This aberrant regenerative process, together with fibrosis, sets the stage for chronic changes that occur in **cirrhosis.**

4. Liver blood flow

Liver receives blood via two sources: venous flow from the **hepatic portal vein**, which is crucial to performance of the liver's roles in bodily functions; and arterial flow from the **hepatic artery**, which is important for blood oxygenation. These vessels converge within the liver, and the combined blood flow exits via so called **central veins** that drain into the hepatic vein and ultimately the inferior vena cava. The portal vein carries venous blood from the small intestine, rich in freshly absorbed nutrients and sometimes drugs and poisons, and from pancreas, rich in pancreatic hormones (insulin, glucagon, somatostatin) directly to the liver. The portal vein forms a capillary bed that allows individual hepatocytes to be bathed directly in

portal blood. ***In part because of this system of blood supply, the liver is a prime site for metastatic spread of neoplasms, especially from the gastrointestinal tract, breast, and lung.***

The portal blood, being venous in nature, is normally under **low hydrostatic pressure** (about 10 mmHg). Accordingly, there must be little resistance to its blood flow within the liver, allowing the blood to percolate through the sinusoids and achieve maximal contact, for exchange of substances, with hepatocytes. This feature is crucial to the liver's function of uptake from and secretion into the bloodstream and also contributes to the efficiency of the liver as a filter of portal blood. Its loss in cirrhosis results in profound changes in liver blood flow with devastating clinical consequences.

B. TYPES OF LIVER DISFUNCTION:

Most of the clinical consequences of liver disease can be understood either as a failure of one of the liver's four broad functions or as a consequence of portal hypertension, the altered hepatic blood flow of cirrhosis.

1. Hepatocyte disfunction

The pathway and extent of hepatocyte disfunction determine the specific manifestation of liver disease. This happens when normal hepatocellular functions become altered. The four broad liver functions are:

I. Energy generation and substrate interconversion
II. Synthesis & secretion of plasma proteins
III. Solubilizing, transport & storage functions
IV. Protective & clearance function

2. Portal hypertension

When pathologic processes (e.g. fibrosis) result in elevation of normally low intrahepatic venous pressure, blood "backs up" and finds alternative venous routes back to the systemic circulation. Thus, blood from the gastrointestinal tract is no longer filtered - or is filtered less efficiently - by the liver prior to entering the systemic circulation. The consequences of this portal -systemic shunting are:

- Development of engorged blood vessels carrying venous blood bypassing the liver (e.g. **esophageal varices**) and the great risk of gastrointestinal hemorrhage related to them
- **Enlargement of the spleen** as a consequence of elevated portal venous pressure and the subsequent development of hypersplenism - thrombocytopenia and hemolytic anemia because of increased sequestering of elements of the blood in the spleen.

- Loss of protective and clearance functions of the liver
- Loss of enterohepatic circuit of bile components and subsequent bile waste
- Functional abnormalities in renal salt and water homeostasis

MANIFESTATIONS OF LIVER DISFUNCTION

Whether due to hepatocyte disfunction or portal-systemic shunting, prominent features of liver disfunctions are manifestations of failure of normal functions. An understanding of these mechanisms offers insights into the probable cause of illness in a patient with acute or chronic liver disease.

I. DIMINISHED ENERGY GENERATION AND SUBSTRATE INTERCONVERSION

I.1. PROTEIN METABOLISM - Amino acid and ammonia metabolism

Aminoacid metabolism

Through a variety of anabolic and catabolic processes, the liver is the major site of amino acid interconversion. Amino acids utilized for hepatic protein synthesis are derived from dietary protein, metabolic turnover of endogenous proteins (primarily from muscle), and direct synthesis in the liver. Most of the amino acids entering the liver via the portal vein are catabolized to urea (except for the branched chain amino acids leucine, isoleucine, and valine). A lesser amount enters into the general circulation as free aminoacids. In addition, amino acids are utilized for the synthesis of liver intracellular proteins, plasma proteins, and special compounds such as glutathione, glutamine, taurine, carnosine and creatine.

- Disruption of normal aminoacid metabolism may be reflected in altered plasma aminoacid concentrations.

In general, the levels of the **aromatic aminoacids** normally metabolized by the liver (as well as methionine) are elevated, while those of the branched chain amino acids , largely utilized by the skeletal muscle, tend to be normal or depressed. It has been suggested that an alteration in the ratio of these two types of amino acids plays a role in the development of hepatic encephalopathy.

With severe liver damage (e.g. massive hepatic necrosis), utilization of aminoacids is impaired, free amino acids in the bloodstream increase, and an "overflow" type of **aminoaciduria** may occur.

Ammonia detoxification

Urea production provides a means for disposal of ammonia, the toxic product of nitrogen metabolism. Disruption of this process is of particular clinical importance in the patient with severe acute and chronic liver disease where urea synthesis is often depressed, leading to an accumulation of NH_3, usually with a significant reduction in

blood urea level, an ominous sign in liver failure. This finding may be obscured by superimposed renal impairment, which often develops in the patient with severe hepatic failure. Urea is mostly excreted by the kidney, but approximately 25 percent will diffuse into the intestine where it is converted to NH_3 by bacterial urease. The intestinal production of ammonia also occurs from bacterial deamination of unabsorbed amino acids and of protein derived from diet, exfoliated cells or blood in the gastrointestinal tract. Gut NH_3 is absorbed and transported to the liver via the portal vein, where it is again converted into urea.

Elevated levels of blood NH_3 generally correlate with the degree of encephalopathy.

I.2. LIPID METABOLISM

I.2. a. Fatty acids and triglicerides

Under normal conditions, most of the fatty acids taken up by the liver and esterified to triglicerides are derived from the adipose tissue or the diet. Some fatty acids (especially saturated ones) are synthesized by the liver from acetate. The fatty acids may be than converted enzymatically to triglicerides, esterified with cholesterol, incorporated into phospholipids, or oxidized to CO_2 or ketone bodies. Most of the triglicerides is produced for the export, but in order to be secreted it must be converted to lipoproteins by combining with relatively specific apoprotein moieties. This emphasizes the importance of protein synthesis for the release and secretion of triglicerides from the liver. Lipid accumulation may occur because of decreased apoprotein synthesis. This situation, called fatty liver, occurs in patients with protein calorie malnutrition and due to toxins such as carbon tetrachloride, phosphorus, or ethionine, as well as following excessive doses of antibiotics such as tetracycline that can inhibit protein synthesis.

Also, an increased influx of fatty acids mobilized from adipose tissue due to drugs (e.g., ethanol or glucocorticoids) or secondary to diabetic ketosis may lead to fatty liver. Similarly, increased levels of fatty acids in the liver, either from enhanced fatty acid synthesis or from decreased fatty acid oxidation, may lead to increased triglicerides formation.

I.2.b. Cholesterol and bile acids synthesis is carried out primarily by the liver. Cholesterol exists either free or combined with fatty acids in the form of cholesterol esters; in plasma are found primarily in association with β lipoproteins (LDL). The plasma and liver also contains lecithin-cholesterol acyltransferase (LCAT or ACAT), an enzyme involved in the conversion of free cholesterol to its esterified form. Since there is exchange of free cholesterol between tissues, changes in plasma cholesterol levels reflect changes in total body cholesterol. *However, decreases in plasma*

cholesterol esters reflect hepatic damage and impaired hepatic cholesterol esterification.

Severe liver injury often leads to a decrease in total serum cholesterol levels, including both free and esterified fractions. This may be due to decreased synthesis of cholesterol and cholesterol esters, decreased apoprotein synthesis or both.

In **cholestasis** (either intra or extrahepatic) total serum cholesterol often increase strikingly. Disorders of cholestasis are associated with marked abnormalities of lipoprotein metabolism. In primary biliary cirrhosis there are **pronounced elevations in serum free cholesterol and LDL**; conversely, serum **HDL is reduced** and may disappear from the serum in patients with long-standing disease. Also, decreased LCAT levels are correlated with the appearance of an abnormal LDL, referred to as **lipoprotein X (LP-X).** The overall increase in total serum cholesterol may be the result of regurgitation of bile salts, cholesterol, and LP-X into the venous blood as well as the result of increased cholesterol synthesis in the liver.

I.3. CARBOHYDRATE METABOLISM

The liver functions to maintain normal levels of blood sugar by a combination of glycogenogenesis, glycogenolysis, glycolysis, and gluconeogenesis. These pathways are regulated by a number of hormones including insulin, glucagon, growth hormone, and certain catecholamines. In the fasting state, the liver contributes to glucose homeostasis by glicogenolysis and gluconeogenesis in response to hypoinsulinemia and hyperglucagonemia.

Abnormalities of glucose homeostasis are common in cirrhosis. Most frequently **hyperglycemia and glucose intolerance** are observed. Glucose intolerance is associated with normal or increased levels of plasma insulin, suggesting that *insulin resistance rather than insulin deficiency* may be responsible. One of the factors that may play a role in the apparent insulin resistance is *an absolute decrease in the liver ability to metabolize a glucose load because of a decrease in functioning hepatocellular mass*. There is also evidence that response to insulin is diminished due to both *receptor and postreceptor defects in the hepatocytes* of patients to cirrhosis. In addition, both hyperinsulinemia and hyperglucagonemia may be present due to *decreased hepatic clearance of these hormones resulting from portal-systemic shunting.*

Patients with cirrhosis may also **have elevated serum lactate** levels reflecting the decreased capacity of the liver to utilize lactate for gluconeogenesis.

Hypoglicemia, although more common in acute fulminant hepatitis, may also be seen with end-stage cirrhosis. It may be due to decreased hepatic glycogen stores, diminished glucagon responsiveness (and secondary diminished gluconeogenesis), or decreased capacity to synthesize glycogen due to extensive parenchymal destruction.

II. DIMINISHED SYNTHESIS & SECRETION OF PLASMA PROTEINS

The clinical significance of liver protein synthesis and secretion derives from the wide range of functions carried out by these proteins.

One of the clinically most important derangements in protein metabolism is the development of **hypoalbuminemia**, which results largely from reduced synthetic activity. Decreased synthesis may be caused by a decrease in the number as well as the functions of hepatocytes. To some extents the body attempts to compensate for decreased albumin synthesis by reducing the rate of degradation. Attempts to raise the serum albumin level by intravenous infusion are often futile because this compensatory mechanism can be blunted and the decrease in albumin degradation may not occur. The degree of hypoalbuminemia is also augmented in the patient with ascites, in which large amounts of body's albumin are present in the ascitic fluid.

Other proteins produced by the liver include many of the **blood-clotting factors:** fibrinogen, prothrombin, and factors V, VII, IX, and X as well as inhibitors of both coagulation and fibrinolysis.

Factors II, VII, IX, and X are vitamin K-responsive and are dependent upon normal intestinal fat absorption.

As expected, severe liver disease leads to reduced synthesis of prothrombin, a vitamin K depending clotting factor. The presence of malnutrition, the use of broad spectrum antibiotics, or concomitant impairment of fat absorption due to reduction in intestinal bile salt concentration (e.g. cholestasis) may accentuate hypoprothrombinemia by decreasing the amount of vitamin K that can be absorbed by the intestine. In these situations, prothrombin levels may at least be partially corrected by parentheral vitamin K administration. However, when the coagulopathy results from impaired hepatocellular function and not cholestasis or intestinal factors, exogenous vitamin K is unlikely to correct or improve prothrombin synthesis. The vitamin K-dependent clotting proteins have a substantially shorter serum half-life than albumin; therefore, hypoprothrombinemia usually precedes the development of hypoalbuminemia. In cirrhosis, coagulopathy may be further aggravated by the thrombocytopenia resulting from hypersplenism.

It is unusual for fibrinogen to be reduced significantly, unless there is an associated disseminated intravascular coagulation (DIC). For unclear reasons, the damaged liver may actually produce increased amounts of fibrinogen as well as other proteins collectively **designated acute-phase reactants** (C-reactive protein, haptoglobin, ceruloplasmin and transferrin). The latter are produced both in response in liver injury and in association with systemic illnesses such as cancer, rheumatoid arthritis, bacterial infections, burns, and myocardial infarction.

III. LOSS OF SOLUBILIZING & STORAGE FUNCTIONS

III.1. Disordered bile secretion

The clinical significance of bile synthesis can be seen in the prominence of **CHOLESTASIS** - failure to secrete bile in many forms of liver disease. Cholestasis can occur as a result of extrahepatic obstruction (e.g. from a gallstone in the common bile duct) or of the selective disfunction of the bile synthetic or transport machinery in the hepatocytes themselves (e.g., from a reaction to certain drugs). The mechanism responsible for cholestatic drug reactions are not well understood. Regardless of the mechanism, however, the clinical consequences of severe cholestasis may be profound: A failure to excrete bile results in a failure to solubilize substances such as dietary lipids and fat-soluble vitamins, resulting in malabsorbtion and deficiency states.

The solubilization of bile works both to excrete and to absorb substances. Thus, in cholestasis, endogenous substances that are normally excreted via the biliary tract can accumulate to high levels. One substance is bilirubin, a product of heme degradation. The build-up of bilirubin results in **jaundice** or **icterus** (yellow discoloration of scleras and skin). In the adult, the most significant feature of jaundice is that it serves as a readily monitored index of cholestasis, which may occur alone or with other abnormalities in hepatocyte disfunction (i.e., as a part of the presentation of acute hepatitis). Similarly, cholesterol is normally excreted either by conversion into bile salts or by forming complexes, termed micelles, with pre-existing (recycled) bile salts. In cholestasis, the resultant build-up of bile salts can lead to their deposition in the skin, manifested as intense itching, or **pruritus**.

III.2. IMPAIRED DRUG METABOLISM AND EXCRETION

Hepatic blood flow, protein binding, and the intrinsic capacity of liver to eliminate a drug are all primary determinants of **hepatic drug clearance**. The liver has an important role in the metabolism of many exogenous drugs and endogenous hormones by virtue of several enzyme systems involved in biochemical transformations. In most cases, this metabolism involves the conversion of **lipophilic** (hydrophobic substances which are difficult to excrete from cells because they tend to partition into cellular membranes) into more **hydrophilic** substances. This process involves catalysis of covalent modifications to make the substance more charged, so that it will partition more readily into an aqueous medium or at least be solubilized sufficiently in bile. As a result of these processes, collectively called **biotransformations**, some substances so modified can be excreted directly in the urine while others are transported into the bile for excretion in feces.

Biotransformation generally occurs in two phases:

- **Phase I reactions** involve oxidation-reductions in which an oxygen containing functional group is added to the substance to be excreted.

While oxidation itself does not necessarily have a major effect on water solubility, it usually introduces into the drug a reactive "handle" that makes possible other reactions which do render the modified substance water-soluble.

- **Phase II reactions** usually involve covalent attachment of the drug to a water-soluble carrier molecule such as sugar glucuronic acid or the peptide glutathione.

Unfortunately, phase I oxidation reactions often convert mildly toxic drugs into more toxic reactive intermediates, which facilitates their conjugation by phase II enzymes.

Two features of the mechanisms of drug detoxification are of particular clinical importance:

- One is the phenomenon of **enzyme induction**. It is observed that the presence in the bloodstream of any of the large class of drugs inactivated by phase I enzymes increases the amount and activity of these enzymes in the liver. This property of enzyme induction makes physiologic sense but can have undesired effects as well. *A patient who chronically consumes large amounts of a substance that is metabolized by phase I enzymes (e.g. ethanol) will induce high levels of these enzymes and thus speed up the metabolism of other substances metabolized by the same detoxifying enzymes resulting in subtherapeutic blood levels of drugs.*
- A second clinically important phenomenon in drug metabolism emerges from that the **phase I reactions often convert relatively benign compounds into more reactive and hence more toxic ones.** Under certain conditions when phase II reactions are impaired (e.g. glutathione deficiency from inadequate nutrition), enhanced phase I enzyme activity can cause increased liver injury. This is because the products of phase I reactions, in the absence of glutathione, may react with and damage cellular components. Such damage can rapidly kill a hepatocyte.

Thus, the combined effects of certain common conditions can make the individual abnormally sensible to the toxic effects of drugs. For example, the combination of induced phase I activity (e.g. due to alcoholism) with low phase II activity (e.g. due to low glutathione levels from nutritional deprivation) can result in heightened generation of reactive intermediates with an inadequate capacity to conjugate and detoxify them.

That there may be varying degrees of impairment in the hepatic uptake, detoxification, and excretion of certain drugs is important in the clinical management of patients with chronic liver disease.

- **Portal-systemic shunting** of blood may decrease the "first pass effect" of drugs absorbed in the gut.
- **Altered intrahepatic hemodinamics** due to a disordered liver architecture (in cirrhosis) may also reduce the rates of hepatic drug clearance.
- **Hypoalbuminemia** will permit drugs usually bound to albumin to be present in increased concentrations of their unbound form in the circulation and extracellular spaces; this may result in an increased activity of such drugs.
- **A decrease in the amount of function of microsomal enzymes** responsible for phase I and phase II reactions will result in slower rates of drug inactivation and elimination.

This will lead to:

- Decrease dosage requirements and a
- Narrowing of the range between therapeutic and toxic drug levels

Finally, the patient with chronic liver disease may demonstrate **alterations in the pharmacological effects** of drugs in addition to or independent of changes in their pharmacokinetics such as increased central nervous system sensitivity to opiates and other sedatives.

III.3. Altered hepatic binding and storage functions

Liver disease influences the liver's ability to store various substances. As a result, patients with liver disease have a high risk of development certain deficiency states such as **folic acid** and **vitamin B_{12}** deficiency. Since these vitamins are needed for DNA synthesis, their deficiency results in **macrocytic anemia**, a common finding in patients with liver disease.

IV. LOSS OF PROTECTIVE AND CLEARANCE FUNCTIONS

IV.1. Clearance of bacteria and endotoxin

Clearance of bacteria by Kupffer cells of the liver is the final line of defense in keeping gut-derived bacteria out of the systemic circulation. Loss of this capacity in liver disease due to portal-systemic shunting may help to explain why, in patients with severe liver disease, infections can rapidly decompensate into sepsis.

IV.2. Altered ammonia metabolism

Impairment of the liver ability to detoxify ammonia to urea leads to **hepatic encephalopathy**, manifested as an altered mental status. This may be an early manifestation of acute fulminant hepatitis with massive hepatocellular disfunction even before the development of maximal hepatocellular necrosis or a final step in

progressive chronic liver disease with diminished hepatocyte functional capacity. Most often it is the consequence of an increased ammonia load in a patient with marginal liver function or significant portal -systemic shunting.

The mechanism known to lead to increased blood NH_3 levels in the patients with cirrhosis include:

- If there is excessive nitrogenous material in the intestine (from bleeding or dietary protein), excessive amounts of NH_3 will be formed by bacterial deamination of aminoacids.
- If renal function declines (as in hepatorenal syndrome), blood urea rises, leading to increased diffusion of urea into the intestinal lumen, where bacterial urease converts it to NH_3.
- If renal function declines (as in hepatorenal syndrome), blood urea rises, leading to increased diffusion of urea into the intestinal lumen, where bacterial urease converts it to NH_3.
- If hepatic function is significantly depressed, diminished urea synthesis may occur with a resultant decrease in the removal of NH_3.
- If alkalosis (often due to central hyperventilation) and hypokalemia accompany hepatic decompensation, there may be a decrease in the renal availability of H^+ ions; as a result, the NH_3 produced from glutamine by the action of renal glutaminase is permitted to enter the renal vein (rather being excreted as NH_4^+) leading to increased peripheral blood NH_3 levels. In addition, hypokalemia itself leads to increased NH_3 production.
- If portal hypertension is present and anastomoses exist between the portal and systemic venous channels, these portal-systemic shunts will allow NH_3 from gut to bypass hepatic detoxification, leading to elevated blood NH_3 levels.
- Because unionised NH_3 crosses membranes more readily than NH_4^+ ions, alkalosis favors the entry of ammonia into the brain (with subsequent changes in cell metabolism) by shifting the equilibrium of the following reaction to the right:

$$NH_4^+ + OH^- \longleftrightarrow NH_3 + HOH$$

As a result, alkalosis not only increases peripheral blood NH_3 levels by renal mechanisms but also increases tissue levels by influencing the diffusion of NH_3 across the membranes.

IV.3. ALTERED HORMONE CLEARANCE

In addition to its role in the metabolism of diverse pharmacological agents, the liver is also responsible for inactivation or modification of several hormones as insulin, glucagon, thyroxine, and steroid hormones. Therefore, chronic liver disease may be accompanied by signs of apparent hormonal imbalance. The mechanisms of this imbalance are the same mechanisms involved in the impairment of drug metabolism (see above).

Abnormalities in estrogen (and testosteron) metabolism are believed to be involved in the development of spider angiomas, loss of axillary or pubic hair, and testicular atrophy frequently seen in patients with chronic liver disease. In addition, increased portal-systemic shunting of testosterone and androstenedione secondary to portal hypertension may lead to development of ginecomastia in cirrhotic males due to increased peripheral conversion to estradiol and estrone. The net effect is an elevation of blood estrogens, which in turn alters hepatocyte protein synthesis and secretion. Synthesis of some hepatic proteins increases while synthesis of others is diminished. Feminization and inhibition of gonadal-pituitary-hypothalamic axis occur.

SODIUM & WATER IMBALANCE

Patients with liver disease often display renal abnormalities and complications, most commonly sodium retention and difficulty in excreting water.

ASCITES:

Ascites is the presence of excess fluid in the peritoneal cavity. Patients with ascites develop physical examination findings of increasing abdominal girth, a fluid wave, a ballotable liver, and shifting dullness. The pathogenesis of ascites is complex (see figure):

- **Portal hypertension**: elevated pressure within the sinusoids increases the volume of flow in the lymphatic vessels at the expense of flow into the central vein. Eventually, flow into the hepatic lymphatics exceeds its capacity for drainage, resulting in overflow of lymphatic fluid in the peritoneal space.
- **Decreased serum albumin** and consequent loss of colloid osmotic pressure within the vascular space also favor the extravasation of fluid from plasma to peritoneal cavity, and thus ascites is infrequent in patients with cirrhosis unless both portal hypertension and hypoalbuminemia are present.

- **Retention of excess sodium by the kidney**

Two theories have been proposed to explain this sodium and water retention by the kidney:

The **"underfilling" theory** suggests that the primary abnormality is inappropriate sequestration of fluid within the splachnic vascular bed due to portal hypertension and a consequent decrease in effective circulating volume According to this theory, an apparent decrease in intravascular volume (underfilling) is sensed by the kidney, which responds by retaining salt and water. **The "overflow" theory** suggests that the primary abnormality is inappropriate renal retention of salt and water in the absence of volume depletion.

Patients with ascites fail to excrete a water load in a normal fashion. They have increased sodium reabsorption by both proximal and distal tubules, the latter due largely to **secondary hyperaldosteronism** and increased plasma renin activity. Sodium retention may be further exacerbated by intrarenal endothelin-mediated vasoconstriction and intrarenal redistribution of blood flow.

C. LIVER FAILURE

Liver failure reflects the destruction of overall hepatic function. This may come about through the insidious action of a chronic progressive disorder, by repetitive discrete bouts of parenchymal damage, or in some cases by sudden and massive destruction of hepatic cells. Whatever the sequence, loss of hepatic functional capacity must exceed 80 to 90% before hepatic failure ensues. In many cases, intercurrent disease, such as gastrointestinal bleeding, systemic infection, electrolyte disturbances, or severe stress (major surgery, heart failure), tips the balance toward decompensation when the functional reserve is precarious.

Many disorders can lead to hepatic failure. The major disorders having such potential can be divided into three categories:

- Ultrastructural lesions that do not produce overt liver cell necrosis: Reye's syndrome. acute fatty liver of pregnancy, tetracycline toxicity.
- Chronic liver disease: Relentless chronic hepatitis, cirrhosis, inherited metabolic disorders.
- Massive hepatic necrosis: Fulminant viral hepatitis; massive toxic damage as from acetaminophen, halothane, monoamine oxidase inhibitors used as antidepressants; and mushroom poisoning (e.g. Amanita species).

Whatever the underlying condition, the clinical features of hepatic failure are much the same, with characteristic signs and symptoms (see the table at the end):

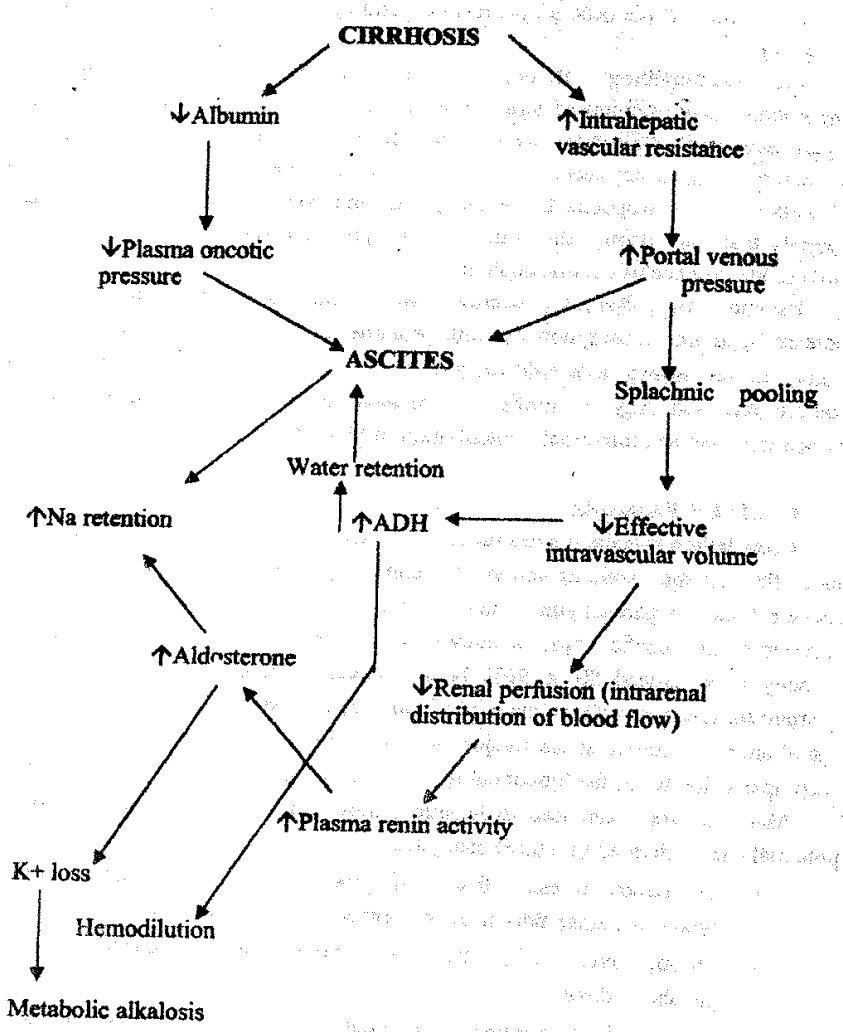


Figure no. 29
Water, electrolyte and acid-base imbalance in cirrhosis

HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy is regarded as a metabolic disorder of the central nervous system and neuromuscular system. In the great majority of instances, there are only minor morphologic changes in the brain. It is manifested by waxing and waning alteration in mental status ranging from subtle alteration to profound obtundation. Cognitive changes include a full spectrum of mental abnormalities, ranging from mild confusion, apathy, agitation, euphoria, restlessness, and reversal of the day-night sleep pattern to somnolence, marked confusion and even coma. Motor changes range from fine tremor, slowed coordination, and asterixis to decerebrate posturing and flaccidity.

Asterixis is a phenomenon of intermittent myoelectrical silence manifested by many muscle groups and enhanced by fatigue.

Two physiologic factors appear to be important in the genesis of this disorder:

- Shunting of the blood around the liver, as occurs from portal-systemic connections that develop in the course of advanced cirrhosis or after surgical portocaval anastomosis, and
- Severe loss of hepatocellular function.

The net result is exposure of the brain to an altered metabolic milieu, the specifics of which are not clear yet.

- One proposed mechanism postulates that the encephalopathy is caused by **toxins such as ammonia,** derived from metabolic degradation of urea and protein in the gut; glutamine, derived from degradation of ammonia; or mercaptans, derived from sulphur-containing compounds in the gut. Increased levels of ammonia, glutamine, and mercaptans can be found in the blood and cerebrospinal fluid. However, blood ammonia and spinal fluid glutamine levels correlate poorly with the presence and severity of encephalopathy.
- Alternatively, there may be impairment of the normal blood-brain barrier, rendering the central nervous system susceptible to various noxious agents. Increased levels of other substances, including metabolic products such as **short-chain fatty acids** and **endogenous benzo-diazepine-like metabolites**, have also been found in blood.
- A third proposed mechanism postulates a role for **GABA**, the principal inhibitory neurotransmitter of the brain. GABA is produced in the gut, and increased levels are found in the blood of patients with liver failure.
- A fourth proposal postulates that there is an increased entry of aromatic aminoacids into the central nervous system, resulting in increased synthesis of **false neurotransmitters** such octopamine and

decreased synthesis of normal neurotransmitters such as norepinephrine.

HEPATORENAL SYNDROME

Hepatorenal syndrome refers to the appearance of renal failure in patients with severe liver disease, in whom there are no intrinsic morphologic or functional causes for the renal failure. Kidney function promptly improves if hepatic failure is reversed. The appearance of this syndrome is typically heralded by a drop in renal output associated with rising blood urea and creatinine. The ability to concentrate urine is retained, with a hyperosmolar urine devoid of proteins and abnormal sediment and surprisingly low in sodium (in contrast to renal tubular necrosis). Renal failure may rapidly progress to death in acute fulminant or advanced chronic hepatic disease. Alternatively, borderline renal insufficiency (serum creatinine 2 to 3 mg/dL) may persist for weeks to months, as in cirrhotic patients whose ascites is refractory to diuretic therapy.

The favored theory to explain this syndrome is reduction of renal blood flow, particularly to the cortex, the result of vasoconstriction. This is accompanied by a decreased glomerular filtration rate and avid renal retention of sodium. A speculated role for nitric-oxide mediated peripheral arterial vasodilation combined with sympathetic nervous system and endothelin-mediated renal vasoconstriction has been proposed to explain the salt and water retention of cirrhosis. Those same mechanisms, in extreme case, may give rise to the hepatorenal syndrome.

Table 29 - Major clinical features of hepatic failure

Clinical feature	Basis
Jaundice	Total bilirubin metabolism is deranged, conjugated hyperbilirubinemia predominates
Hypoalbuminemia	Reduced synthesis and secretion of albumin
Coagulopathy	Reduced synthesis of clotting factors
Disseminated intravascular coagulation	Activation of Hageman factor, inadequate clearance of activated factors
Hyperammonemia	Defective urea cycle
Fetor hepaticus	Inconstant, formation of mercaptans in gut
Increased serum level of hepatic enzymes	Seen only in active liver necrosis; level of increase correlates with the level of necrosis
Gynecomastia, testicular atrophy, palmar erythema, and spider angiomas of the skin	Related to hyperestrogenism
Hepatic encephalopathy	discussed in the text
Hepatorenal syndrome	discussed in the text
Coma	Usually follows encephalopathy, precedes death

II.4. Pathophysiology of renal disorders

Near constancy of the composition of the internal environment, including the volume, tonicity and compartmental distribution of the body fluids, is a state essential to survival. It requires the continuous excretion of any substances and the greatest responsibility for solute and water excretion is borne by the kidneys.

The volume of urine excreted per day is the small residuum of three processes, namely:

- ultrafiltration of more than 180 l per day (aproximately 125mL/ min) across glomerular capillaries
- reabsorbtion of more than 99% of this ultrafiltrate by transport processes operating in the renal tubules
- tubular secretion of any substances

II.4.1. Abnormalities of the glomerular filtration

Urine formation begins with the elaboration of a protein-free ultrafiltrate of plasma across the walls of the glomerular capillaries.The barrier separating blood from the lumen of the nefron consists of three layers:

- capillary endothelium
- basement mebrane
- epithelium of the Bowman space, formed by podocytes

These layers form a complicated sieve controlling glomerular permeability, thus the glomerular filtrate is a protein free plasma.

The rate of glomerular filtrate production is dependent on:

- the balance of pressure acting across the capillary wall (glomerular effective pressure)
- the rate at which plasma flows through the glomeruli (renal blood flow)
- the permeability and the total surface of the glomerular filtration membrane

The effective pressure is influenced by the following factors:

- afferent arteriolar hydrostatic pressure(normally, 70- 75mmHg)
- plasma protein oncotic pressure (25-30 mmHg)
- pressure within th renal tubules equating the pressure in the Bowman space (5-10mmHg)

The balance of pressure acting across the capillary wall (the effective pressure of filtration) is normally, 30-40 mmHg.

Urea and creatinine concentrations in serum are often measured to assess the glomerular filtration rate (GFR). They are produced at a constant rate and they undergo glomerular filtration but are not reabsorbed extensively by the renal tubules. An increase in their serum concentrations, termed azotemia, occurs as the GFR falls.

The usual consequences of glomerular damages are:

- variations in urinary output
- changes in the urinary constituents

CHANGES OF THE URINARY OUTPUT

Normally, adults void between 700- 2000ml daily.

Changes of the urinary output are:

- polyuria: a daily urinary volume more than 2500ml
- oliguria: a daily urine volume less than 500ml
- anuria: a severe diminution of the urinary output, less than 100ml

Polyuria

A resonable definition of polyuria is a urine volume above 3 liters per day, but this may be qualified to exclude normal individuals who desire a large fluid intake and therefore form large volume of urine. It must be distinguished from urinary frequency, the frequent voiding of small volumes.

Causes of polyuria:

- inadequate renal water conservation
- primary polydipsia

The first condition is secondary to the following causes:

1. diabetes insipidus: the term is applied to situations in which inadequate renal water reabsorbtion causes polyuria and secondary thirst:
   - vasopresin insufficiency (central diabetes insipidus), due to inflammatory or neoplastic conditions, trauma, hypophysectomy or idiopathic conditions
   - renal unresponsivenes to vasopresin (nephrogenic diabetes insipidus), ussualy aquired from renal disorders: interstitial renal diseases (pielonephritis, obstructive uropathy, multiple myeloma), analgesic nephropathy
2. solute diuresis: excessive filtration of a poor rebsorbed solute such as glucose (diabetes mellitus), manitol (an osmotic diuretic) or urea (recovery phase of acute renal failure or compensated stage of chronic renal failure) can depress rebsorbtion of water in the proximal tubule and cause their loss in the urine, producing polyuria.
3. natriuretic syndromes:
   - salt- losing nephritis: tubulointerstitial diseases in which it is an excessive chronic Na loss

- diuretic phase of acute tubular necrosis, in which Na and water losses are very large

Primary polidipsia: some people drink enough water every day because of predilection psychiatric disorders or a specific lesion in the brain. During deliberate polydipsia, extrarenal fluid volume is normal or high and vasopresin secretion is reduced because serum osmolarity tends to be near the lower limit. Reabsorbtion of water from the end distal convoluted tubule and collecting ducts is reduced so that all the water can be excreted in the urine.

OLIGURIA and ANURIA

Oliguria refers to a urinary volume insufficient to sustain life, ussualy less than 500 ml per day in an adult of average size. Anuria is the absence of urine flow or a urine volume less than 100 ml/ day. Both conditions are determined by 3 categories of causes:

- prerenal causes, all associated with diminution of the renal blood flow: severe dehydration, edema forming states (nephrotic syndrom or cirhosis), systemic hypotension, hemorhages. Decreased glomerular filtration rate of individual functionig nephrons is associated by a normal tubular function. Thus an important response of the normal kidney to a severe extracellular fluid volume depletion is the reabsorbtion of an increased fraction of the reduced amounts of NaCl and water that enter the tubules, as a result of vasopresin and aldosteron secretion. Urinary sodium concentration is decreased. When those factors have a very long time action, they produce ischemic damages of the tubules sufficiently to reduce their responsivenes to ADH and aldosteron and thier reabsorbtive function, producing acute tubular necrosis (intrinsic renal failure). The urine Na and osmolarity are increased.
- postrenal causes: postrenal anuria is a term often applied when acute obstruction of any portion of the urinary tract causes an increase of the presure within the Bowman space and a decrease of the filtration pressure
- renal causes, refears as acute glomerular injuries (swelling of endothelial cells and inflammatory infiltration results in decreased permeability and diminution of total filtering surface area of the glomerular filtration membrane) or ischemic tubular necrosis

Changes of the urinary constituents

Because of their size, the blood cells and the proteins do not normally pass thorough the glomerular filter. Thus the fluid in Bowman space is a protein-free filtrate of plasma. Permeability of the glomerular filtration membrane is increaesd in many renal diseases in which it fail to function as a filter, permiting blood cells and plasma proteins to leak through the injured capillaries and endothelial cells to be excreted in the urine.

Reduced nephron number - increased SNGR	- anatomic and functional hypertrophy of the remaining nephrons; with marked reduced nephron number, total GFR depend more and more on expansion of the extracellular volume	- chronic pyelonephritis - surgical loss of renal tissue	- oliguria is rare if total GFR is below 5% of normal	- reflect tubular damages: less than 300 mosm/kg	- more than 40 mmol/L	less than 1012
- normal SNGR	- if glomerulus is the primary site of damage→ total GFR falls but is not supported by elevated SNGR→ tubular reabsorbtive capacities are normal	- chronic glomerulopa-thies	- oliguria is rare	- less than 350mosm/kg	- more than 40 mmol/L	
- reduced SNGR	- any circumstances that can reduce renal blood flow in a patient with reduced number of functioning nephrons→ alteration of the urine chemistry like in prerenal causes but to a lesser extent	- causes of prerenal azotemia in a patient with chronic renal disorders	- common	- less than 290 mosm/kg	- more than 20 mmol/L	

Table 21 - The principal mechanisms of oliguria

Mechanism of reduced GFR	Compensatory mechanisms	Clinical examples	Oliguria	Urine osmolarity	Urine Na concentration	Urine specific gravity
Reduced single nephron GFR (SNGR)						
- prerenal azotemia	- depletion of the extracellular fluid→ vasopresin and aldosteron secretion→ maximal osmotic concentration of urine, due to water and Na reabsorbtion	- edema forming conditions - dehydration - systemic hypotension - renal vascular obstruction - diuretic therapy	- always present	more than 500 mosmol/kg	less than 20 mmol/L	more than 1018
- postrenal azotemia	- urinary obstruction	- uric acid or sulfamide crystals - obstruction of the lower urinary tract				
- renal azotemia	- decreased of the filtration area and contraction of the mesangial cells	- glomerulopathies				
	- abolish of the reabsorbtive capacities of the renal tubules	- acute tubular necrosis due to prolonged renal ischemia or nephrotoxic agents	common, but not aloways	less than 350 mosm/kg	more than 40 mmol/L	less than 1012

Proteinuria

The circulating plasma proteins are normally excluded from passage through the glomerular barrier. There are four factors who serve as major barriers to protein filtration:

- glomerular capillary basement membrane is a dense layer offering resistance to large molecules more than 5 nm
- glomerular capillary endothelial calls form a barrier penetrated by pores of about 100 nm diameter, that hold back cells and macromolecules
- the slitlike diaphragms that connect adjacent epithelial cell foot processes
- electrostatic factors: albumin molecules behaves as a polyanion in physiologic solution and is therefore retarded by the anionic glycoproteins in the various component layers of the glomerular wall.

Normally, adults may excrete up to 150mg proteins daily. Of this, only 10-15 mg are albumins, the rest is composed of over 30 different plasma proteins and of glicoproteins that derive from the renal cells. Tamm- Horsfall mucoprotein is produced by the cells of the ascending limb of the loop of Henle and is excreted at the rate of 25 mg per day. Ussual methods do not identify this level of proteinuria, so we can say that the preoteinuria is absent. Proteinuria is usually detected by urine dipsticks, that register more than 50 mg of proteins per liter of urine.

Daily excretion of more than 150 mg proteins is termed pathologic proteinuria.

Mechanisms of proteinuria:

- glomerular proteinuria: glomerular diseases can disrupt any of the above filtration barriers

- injuries limited to the polyanion glicoproteins tend to produce selective losses of anionic proteins such as albumin, causing a selective proteinuria
- extensive injuries that involves the entire basement membrane, not only its polyanion components , cause excretion of very large proteins, resulting in nonselective proteinuria; using urinary electrophoresis in order to separate various urinary proteins, nonselective proteinuria has a urinary electrophoresis identical to blood electrophoresis

Glomerular proteinuria may be *intermitent* or *persistent.* Intermitent proteinuria may be due to exercise (it is also associated with hemoglobinuria, hematuria or myoglobinuria), fever, heart failure or standing position (orthostatic proteinuria). The exact significance of intermitent proteinuria is not clear: most conditions are associated with decreased renal perfusion and secondary ischemia of the glomerular filtration membrane. Orthostatic proteinuria may be secondary to excessive lordosis

necessary to maintain a prolonged standing position. Persistent proteinuria is more serious. In this case, a quantitative measurement of protein excretion in 24 hours are useful for diagnosis. The amount of proteinuria may be related to creatinin content in the urine. Normally, the protein/ creatinin ratio is less than 0,1. Heavy proteinuria means more than 2g proteins/ m2/ day or a protein/ creatinin ratio more than 2 (or a protein excretion more than 3,5g/day)

- tubular proteinuria: serum proteins with low- molecular weight less than 40.000 (such as beta2 microglobulin or lysosyme) are filtered by the glomeruli but are reabsorbed efficiently by the tubules. Disease that selectively damage the tubules more than glomeruli, cause excessive excretion of these small proteins: analgesic nephropathy, miscellaneous nephrotoxins (heavy metals, antibiotics), metabolic toxins (hypokalemic or hypercalcemic nephropathy, acute and chronic uric acid nephropathy). The resulting proteinuria is usually mild, between 1-3 g per day.
- overflow proteinuria: elevated plasma concentration of normal or abnormal proteins result in increased glomerular filtration , which exceed the tubular ability to reabsorb them.. Bence- Jones protein is a dimer of two light chains which is secreted by the neoplastic plasma cells in multiple myeloma; if the filtered load rises to exceed tubular reabsorbtive capacity, overflow proteinuria may occur.

Hematuria

The term refears as the presence of blood in the urine.

1) Nephronal hematuria: it demonstrates a significant renal disease associated with increased permeability of the glomerular filtration membrane (glomerular inflammations), tubular injuries, vasculitis localized in the glomerular arteriolles (Henoch- Schonlein syndrom). Blood that enter the tubular fluid can be trapped in a cylindrical mold of gelled Tamm- Horsfall protein to produce red blood cell casts. The presence of RBC casts is a marker of nephronal injury.Usually, nephronal hematuria is associated with significant proteinuria, except focal glomerulonephritis accompanied by reccurent and benign hematuria
2) Isolated hematuria, without significant proteinuria, cells or urinary casts: urinary lithiasis, cancer of the kidney or of the urinary tract, tuberculosis or prostatitis , hypocoagulable states(thrombocytopenia, defficiency of coagualtion factors)
3) Hematuria associated with urinary tract infections: it is associated with leukocyturia and the presence of pathogenic bacteria in concentration above 10 5 per ml.

Casts

Casts are cylindrical structures formed in the tubules (especially in the distal convoluted or in the colector tubule) by the agglutination of proteins (Tamm- Horsfall protein gels when concentrated at a low pH or when exposed to myoglobin, hemoglobin or albumin) and cells. Because of their shape, their presence in the urine is called cylindruria.

Hyaline casts are transparent structures formed by agglutination of albumins and Tamm- Horsfall protein.

WBC and epithelial casts can occur in inflammatory states, such as pyelonephritis. When these cells degenerate, they form granular nonpigmented casts. Epithelial casts may originate from severe damages of the renal tubules in acute tubular necrosis.

RBC casts are formed by the trap of red blood cells in cylindrical mold in nephronal hematuria.

Faty casts contains tubular cells filled with cholesterol-rich lipid droplets and proteins. They are associated with havy proteinuria and lipiduria in nephrotic syndrom.

Broad casts arise in the dilated tubules of enlarged nephrons that have undergone compensatory hypertrophy in response to a reduction of functioning renal mass (chronic renal failure).

4.2. Abnormalities of tubular functions

During passage along the tubule, the glomerular filtrate, initially isotonic and neutral, becomes hypertonic and acid. Within 24 hours, 180 litres of filtrate are reduced to 1,5 litres of urine. Three mechanisms are involved:

- active aborbtion of substances from the filtrate by the tubular epithelium (glucose, proteins)
- passive interchange between the filtrate and the interstitial tissue to maintain osmotic equilibrum
- secretion by the tubular epithelium

Proximal tubule

The main function is active reabsorbtion of sodium, potasium, glucose, aminoacids, phosphates, calcium and uric acid. active reabsorbtion requires energy and thus there is a limit to the maximal capacity of the process, called maximal tubular capacity.

The main disorders of the proximal tubule are:

1. Fanconi syndrom is a constellation of transport defects of the proximal tubule involving aminoacids, glucose, sodium, potasium, calcium and phosphates. The anatomic basis of this tubular disorder is cellular tubular

atrophy of the proximal tubule. The syndrom may be aquired (secondary to cystinosis, amiloidosis) or an autosomal recessive transmited disease.

2. Familial x-linked hypophosphatemic vitamin D-refractory rickets: hypophosphatemia arises in part from decreased tubular reabsorbtion and increased excretion of phosphate . Patients may be symptom-free but usually they have a short height and rachitic bones, due to decreased bone mineralisation.
3. Selective disorders of aminoacid transport

- Hartnup disease: renal and intestinal transport of mono amino monocarboxylic acids is defective. Defficiency of tryptophan limits nicotinamide synthesis and leads to secondary pellagra (erythematous rush appearing after exposure to sunlight)
- Cystinuria is characterised by excessive urinary excretion of the cystine, lysine, arginine. The aminoaciduria results from impaired tubular reabsorbtion of these aminoacids. A similar defect exist in the intestinal mucosa. Overexcretion of cystine predispose to the formation of renal calculi.

4. Renal glucosuria

Criteria for the diagnosis of renal glucosuria are:

- glucosuria in the absence of hyperglicemia
- constant glucosuria with little fluctuation related to diet
- normal storage and utilisation of carbohydrates

Normally, glucose is present in the glomerular filtrate at a concentration equal to that in plasma. It is reabsorbed throughout the proximal renal tubule by a sodium-dependent transport process. Thus glucose does not appear in the urine. The plasma concentration at which filtered glucose begins to escape proximal tubular reabsorbtion is usually around 10mmol/l (180-200mg/dL). Maximal renal reabsobtive capacity is 325mg/ 1,75m2 body surface area, also called maximum tubular transport of glucose. Type A renal glucosuria is characterized by a reduced maximum reabsorbtive capacity.

Distal convoluted tubule

1. Familial nephrogenic diabetes mellitus: the distal and collecting tubules are unresponsive to vasopresin type V2 (ADH) . Unresponsiveness to antidiuretic hormon may by secondary to reduced production of cyclic AMP in the epithelium of the collecting duct, to the inability of cAMP to increase the permeability of colecting duct membranes to water or to a combination of these. Affected persons become dehydrated and hypernatremic.

2. Renal tubular acidosis

In these group of disorders renal excretion of acid is reduced and metabolic acidosis results. Therefore, the kidney reabsorb chloride in unusually large amounts and serum chloride rises to preserve electroneutrality in the extracellular fluid. The results is hyperchloremic acidosis with a normal anionic gap.

- type I renal tubular acidosis (distal type)

The collecting ducts permit excessive back- diffusion of hydrogen ions from the lumen to the blood. The kidney does not lower urine pH normally. Chronic acidosis lowers tubular reabsorbtion of calcium , causing renal hypercalciuria (calcium stones) and secondary hyperparathyroidism. It is accompanied by renal hypercalciuria and hyperkalemia. Diagnosis is made on the following reasons: osteomalacia or rickets, hyperchloremic acidosis, alkaline urine, calcium phosphate stones or nephrocalcinosis.

- type II RTA (proximal), usually occurs as a part of a generalized disorder of the proximal tubule function with a defective of the proximal reabsorbtion of bicarbonate
- type III is a combination of types I and II
- type IV, associated with low urine ammonia excretion rate and high serum potasium level. The most patients have hyporeninemic hypo-aldosteronism: diabetic nephropathy, hypertensive nephrosclerosis or chronic tubulo interstitial nephropathy.

II.4.3. Parthophysiology of nephrotic syndrome

Nephrotic syndrome (NS) is characterized by a severe and prolonged increase in glomerular permeability for proteins. The main futures are:

- proteinuria more than 2g/m2/day (or more than 3,5 g/ 1,73m2 surface of body area per day, or urinary protein concentration of greater than 0.4mg/mmol creatinine, or urinary protein/ creatinine ratio more than 2)
- sustained heavy proteinuria is often associated by hypoalbuminemia less than 3 g/dL
- hyperlipidemia is a frequent accompaniment of the nephrotic state, with hypercholesterolemia and lipiduria
- generalized edema also is frequently present to complete this complex syndrome.

Etiology and classification

1. Primary renal diseases determines the idiopathic NS, frequent in childhood period. This type is subclassified in according to the morphologic features found on

renal biopsy, all of them resulting in increase permeability of the glomerular filtration membrane:

- minimal change disease: this is often reffered to as lipoid nephrosis or foot process disease. In this form, although little or no alterations of the glomerular capillary barriers are demonstrable by light microscopy, diffuse epithelial foot process effacement is evident by electron microscopy.Proteinuria is selective because of loss of crarge selective barrier. The disease is also called minimal change nephritis. it is the most encountered form of idiopathic NS in children , accounting for more than 70- 80% of cases diagnosed before the age of 8.
- other hystological forms of glomerulonephritis may be clinical expressed as NF. The morphological changes include deposites of complement and immune complexes in the glomeruli, hialinisation, loss of foot processes, global sclerosis, proliferation of the mesangial cells. Proteinuria is nonselective because of loss of size selective barrier.

The diagnosis of idiopathic form of NS is arrived at by exclusion of known causes of NS.

1. Secondary NS, as an evolutionary stage of secondary glomerulopathies
   - metabolic: diabetes mellitus (either diffuse and nodular intercapillary glomerulosclerosis) and renal amiloidosis
   - immunologic-induced disorders: systemic erythematous lupus, polyarteritis nodosa, scleroderma or Henoch-Schonlein purpura
   - neoplastic disorders, NS being a paraneoplastic syndrom: Hodgkin lymphoma, leukemias, multiple myeloma, carcinomas (breast, colon, lung, kidney)
   - nephrotoxic agents: nonsteroidal anti-inflammatory drugs (most common), gold, penicillamine, contrast media
   - allergens: insects, snake venoms, poisons
   - infections: poststreptococcal glomerulonephritis, AIDS
   - heredofamilial: congenital NS, Alport syndrome
   - miscellanous: chronic allograft rejection, myxedema, sickle cell anemia, malignant hypertension, heart failure, tricuspid insufficiency, acute pericarditis, thrombosis of the renal veins

Pathophysiology:

Normal glomeruli filters very low level of albumins or globulins. **Proteinuria** is thought to occur through derangements of two mechanisms:

- the charge- selective barrier fails to retain lower-molecular weight proteins; thus . injuries limited to the polyanionic glycoproteins tend to

produce selective losses of anionic proteins, such as albumins.That means selective proteinuria and it occurs usually in minimal change disease.

- the size-selective barrier leaks large protein molecules: extensive injury that involves the entire basement membrane, occuring a nonselective proteinuria

Hypoalbuminemia exist as a consequences of :

- excessive urinary loss
- increased renal catabolism of proteins
- inadequate hepatic synthesis of albumin

The resulting decrease in plasma oncotic presure leads to a disturbances in the Starling forces acting across peripheral capillaries. Intravascular fluid migrates into the interstitial tissue, particularly in areas of low tissue pressure, and **edema** occurs. These disturbances initiate a series of hemodinamic changes to correct the resulting deficit in effective plasma volume. These include:

- activation of the renin- angiotensin- aldosteron system leading to renal sodium and water reabsorbtion
- an alteration in the secretion or in renal response to atrial natriuretic peptide.
- enhanced vasopresin secretion
- stimulation of the sympathetic nervous system

As long as hypoalbuminemia is severe, the salt and water retained cannot be restrained within the vascular compartment, and hence the stimuli to retain salt and water are not abated.

So, patients develop usually hypovolemia, hyperreninemia and secondary hyperaldosteronism and avid renal salt retention, with expanded extracellular fluid volume.

The diminished plasma oncotic pressure appears to stimulate hepatic lipoprotein synthesis and thus hyperalbuminemia is a frequant accompaniment of the nephrotic state. The factors which contribute to the **hyperlipidemic state** are:

- excessive urinary loss of plasma protein factors regulating lipoprotein catabolism such as lipoprotein lipase
- the decreased transformation of VLDL to LDL
- diminution of renal catabolism of lipoproteins

Low density lipoproteis and chilomicrons are elevated, but VLDL and triglycerides are also increased.

An early *clinical sign* of NS, noted by patient, is frothy urine, determined by proteinuria. Other symptoms are:

- anorexia

- malaise
- abdominal pain
- edema: exists particularly in areas of low tissue pressure. Most often the edema is mobile- detected in the eyelids in the morning and in the ankles after ambulation. Focal edema refears as pleural effusion, laringeal edema, pericardial effusion, hydroarthrosis, anasarca
- severe plasma volume reduction is associated with postural hypotension, syncope and hypovolemic shock.

Diagnosis involved either urine and blood investigations.

Urine investigations shows:

- severe selective or nonselective proteinuria
- lipiduria with crystals of cholesterol with polarized light microscopy
- Na concentration is decreased in the accumulation phase of nephrotic edema; K has a low concentration
- microscopic hematuria, depending on the hystological type of glomerular disease; it is absent in minimal change disease

Blood investigation shows:

- hypoalbuminemia is detected by quantitative electrophoresis.When edema appears, albumin level is often less than 2,5g/dL in adults and less than 1g/dl in children (chlidren have a better lymphatic outflow which prevent edema formation)
- complement level is decreased especially C3, according to etiology
- fibrinogen level is increased as albuminemia diminishes
- blood urea nitrogen and serum creatinin concentrations vary according to the degree of renal impairement. There are normal in minimal change disease but are increased (as a prove of a decline in glomerular filtration rate with secondary renal failure) in other hystological types
- cellulose acetat eletrophoresis of the serum shows, in additon to diminished albumin level, increases of $\alpha 2$ and β- globulins

Complications

A wide variety of clinical syndroms may develop in prolonged NS:

- nutritional deficiency including protein malnutrition, with brittle hair and nails and stunted growth
- loss of thyroxine- binding globulin may produce abnormalities in thyroid function including a hypothiroidism
- loss of cholecalcipherol- binding protein may lead to a vitamin D defficiency state and secondary hyperparathyroidism and may contribute to the demineralisation of the bones (osteomalacia or rickits)
- enhance urinary excretion of transferin may produce an iron-resistant microcytic hypochromic anemia

- hypercoagulable state: a variety of factors contribute to the enhanced tendency to thrombosis in nephrotic patients:
  - defficiency of antithrombin III, due to urinary loss
  - reduced level or activity of protein C or S
  - impaired fiblinolysis
  - hyperfibrinogenemia
  - enhanced platelet aggregation
  - hyperviscosity of the blood due to hyperlipidemia
- immunoglobulin defficiency, due to urinary loss and hypercatabolism; low- molecular weight complement may be lost in the urine and contribute to defects in the opsonization of bacteria and tendency to severe infections
- various drug- binding proteins (albumins) are decreased, altering the pharmacokinetics and toxicity of many drugs

II.4.4. Pathophysiology of acute renal failure (ARF)

ARF is defined as a rapid deterioration in renal function sufficient to result in accumulation of nitrogenous wastes in the body, with or without oliguria.

The causes of ARF can by grouped in three categories (see table 2):

- prerenal azotemia: decreased renal perfusion
- renal azotemia (renal parenchymal disorders)
- postrenal azotemia (obstruction to urine flow)

Table 22 - Classification of major causes of ARF

Major causes of ARF	***Mechanisms***	***Etiology***
1. Prerenal failure	- hypovolemia	- hemorrhages - burns - dehydration - gastrointestinal fluid loss - renal fluid loss - sequestretion of fluid in the extravascular space
	- low cardiac output	- diseases of myocardium - valvulopathies - cardiac tamponade - arrythmias - pulmonary embolism
	- increased renal/systemic avscular resistance ratio	- systemic vasodilation(sepsis, anaphylaxia) - renal vasoconstriction (hypercalcemia, drugs: epinephrine) - hepatorenal syndrome due to redistribution of the splahnic circulation
	- impairement of renal autoregulatory responces	- cyclooxigenase inhibitors - angiotensine-converting- enzyme inhibitors
	- hyperviscosity syndrom	- multiple myeloma - polycytemia

2. Intrinsic renal failure	- renovascular obstruction	- ATS - vasculitis - emboli - thrombosis
	- diseases of the glomeruli and glomerular microcirculation	- acute glomerulonephritis - lupus - DIC and related forms(hemolytic uremic syndrom) - malignant hypertension
	- acute tubular necrosis	- prolonged ischemia, due to prolonged prerenal causes - toxins
	- interstitial nephritis	- allergic - infectious: pyelonephritis
	- intratubular obstruction	- myeloma proteins - sulphonamides - uric acid
3. Postrenal failure	- ureteric obstruction	- calculi - clott - cancer or cancerous extrinsic compresion - retroperitoneal fibrosis - necrotic papillae
	- bladder or urethral obstruction	- neurogenic bladder - prostatic hyperthrophy

Prerenal azotemia

It si caused by many categories of factors, all of them resulting in diminishe of renal perfusion:

- extracellular volume depletion
  - gastrointestinal liquid loss (vomiting, diarheea)
  - renal water loss (diuretic therapy or marked poliuria due to osmotic factors- decompensated diabetes mellitus with ketone bodies)
  - hemorhages
  - sequestretion of extracellular fluid (pancreatitis, peritonitis)
- marked reduction fo cardiac output (cardiogenic shock, myocarditis, myocardial infarction, severe congestive heart failure)
- peripheral vasodilation (sepsis, anaphylaxis)

Prerenal ARF occurs when it is a decrease in renal perfusion sufficient to lower glomerular capillary perfusion pressure. The syndrom is also due to a functional response to renal hypoperfusion:

- activation of sympathetic nervous system
- activation of renin- angiotensin- aldosteron system
- release of ADH
- secretion of vascular endothelin

Thes are systemic mechanisms which redistributes the cardiac output in order to compensate the decreased effective arterial blood volume.

Several renal mecnanisms combine to maintain glomerular filtration:

- stretch receptors (stimulated by reduction of glomerular perfusion) in afferent arterioles trigger vasodilation
- synthesis of renal vasodilators: prostaglandins and nitricoxid, which preferentially dilate afferent arterioles
- angiotensin *II* induces preferential constriction of efferent arterioles, because of high density of receptors

As a result, intraglomerular pressure is preserved and the fraction of plasma filtered by glomeruli (filtration fraction) is increased.

Prerenal azotemia, if appropriately treated, is readily reversible; inadequated treated, prolonged renal hypoperfusion can elad to ischemic acute tubular necrosis.

Intrinsic renal azotemia are multifactorial:

- acute tubular injuries: ischemia, toxins, radiocontrast agents, hemoglobin, myogloöin
- acute glomerulonephritis
- disseminated intravascular coagulopathy with cortical necrosis
- acute tubulointerstitial nephritis, due to drug allergy (penicilamine, furosemid), diabetes mellitus (papillary necrosis), pyelonephritis
- intrarenal tubular obstruction, due to intrarenal precipitaiton of poorly soluble substances such as uric acid in tumor chemotherapy or multiple myeloma proteins

After exclusion of renal vascular, glomerular and interstitial causes of acute renal failure, there remains a large group of patients commonly referred to as having acute tubular necrosis. The most common causes for acute tubular necrosis are:

- prolonged renal ischemia
- nephrotic agents (heavy metals, aminoglycoside antibiotics)
- myoglobin and free hemoglobin: myoglobinuria, due to extensive trauma with crush injury, is not directly nephrotoxic but tubular obstruction amy cause acute renal failure; ehmoglobin per se is not a potent nephrotoxin but intravascular hemolysis si associated with areleased of a toxic substance from red blood cell stroma.

The mechanisms by which renal hypoperfusion and ischemia impair glomerular filtration include:

1. Reduction of glomerular perfusion and filtrate

Reduced glomerular perfusion results in ischemia of the endothelial cell, with a secondary imbalance between the endothelial-derived vasodilators(nitricoxide, prostacyclin) and release of endothelial-derived vasoconstrictors (endothelin). These

leads to renal vasoconstriction , loss of autoregulatory responses and mesangial cell contraction, with diminishe of the glomerular filtration area. Renal hypoperfusion leads to ischemia of renal tubular cells, especially of proximal tubule. Cellular ischemia causes decrease of ion transport, reabsorbtion and ultimately to cell necrosis.

Epithelial cells of the macula densa detect high level of salts(probably chloride) in the distal tubule, because of impaired proximal tubule reabsorbtion, and stimulate afferent arterioles vasoconstriction by a process termed tubulo-glomerular feed-back, leading to colapse of the glomerular filtration.

2. obstruction of tubules by cells and debris derived from ischemic epithelium

3. backleak of glomerular filtrate through the necrotic epithelium

The kidney is particulary susceptible to nephrotoxic injury by its ability to concentrate the toxins in the medular epithelium and epithelial cells. They may have specific mechanisms of actions. Aminoglycosides disrupt membrane phospholipids. Cisplatin causes mithocondrial injury. Both agents togather with radiocontrast agents and cyclosporine cause renal vasoconstriction.

Postrenal azotemia:

- blader neck obstruction due to prostatic disease
- obstruction of the upper urinary tract requires simultaneous obstruction of both ureters or unilateral ureteric obstruction with severe disease of absence of the controlateral kidney (retroperitoenal fibrosis, absece, tumors, blood clots)

In postrenal ARF ther are two mechanisms:

- decrease of urine excretion who is normally secreted by the kidney
- the increase pressure in the Bowmann space which equals the effective pressure

Clinical course and laboratory findings

The clinical course of ARF can be devided into 3 phases:

- initiating phase
- mainteanance phase
- recovery phase

The initiating phase is the period of time between the precipitating event and the appearance of acute renal failure. Clinical signs are caused by the precipitating factors such as hypovolemia (hypotension, increased pulse rate, decreased jugular venous pressure, oliguria, pale skin, sweating, thirst). Recognition of the initiaying phase is very important since early corection of the cause may prevent the development of the maintainance phase (table 23)

Table 23 - Renal failure indices in differential diagnosis of prerenal from intrinsic renal failure

Indices	Prerenal failure	Intrinsic renal failure
1. Fractional excretion of Na	less than 1	more than 1
2. Urine osmolarity	more than 500 mosm/kg	less than 250 mosm/kg
3. Renal failure index	less than 1	more than1
4. Urine specific gravity	more than 1018	less than 1012
5. Urine Na concentration	less than 10 mmol/L	more than 20 mmol/L

Laboratory findings shows:

- urine osmolarity more than 5oomOsm
- urine sodium less than 20 mmol/l
- urine creatinine/ plasma creatinine ratio is more than 40

The maintainance phase

1. Oliguria has been considered the cardinal feature of the ARF. But, the patient with ATN may be nonoliguric. Urinary elimination of nitrogenous wastes is impaired, and the urine is characterised by: - decreased osmolarity less than 400mOsm
   - urine sodium more than 40 mmol/l
   - urine creatinine/plasma creatinine less than 20
2. Accumulation of nitrogenous wastes in the blood. The magnitude of thes abnormalities depends on whether the patient is oliguric or nonoliguric and on the patient,s catabolic state. Nonoliguric patients have higher levels of glomerular filtration. In catabolic patients (fever, sepsis) daily increments in BUN and serum creatinine may be much higher.
3. Salt and water overload with resulting hyponatremia and increased of extracellular volume. Hyponatremia is caused by:
   - hemodilution
   - excessive water intake
   - gastrointestinal loss

Hyponatremia and overload of the extracellular space cause edema (cerebral and peripheral) and pulmonary congestion.

4. Hyperkalemia is due to:
   - decreased renal elimination, because of diminution of glomerular filtration
   - release of K from the cell in hypercatabolic state
   - tissue distruction
   - hemolysis

- blood transfusion
- cellular shift of K due to acidosis

Hyperkalemia causes:

- muscle weakness
- flacid quadriparesis
- electrocardiographic abnormalities
  - bradycardia
  - recent appearance of left axis deviation
  - peaked T eave
  - prolonged PR interval and QRS complex
  - ventricular fibrillation and cardiac arrest

5. Hyperphosphatemia, due to decreased phosphorus elimination in the presence of continued release of phosphorus from the tissues
6. Hypermagnesiemia: due to impaired excretion of ingested magnesium
   Hypomagnesiemia reflects injuries of the ascending limb of the loop of Henle, the principal site of magnesium reabsorbtion.
7. Hypocalcemia: the reason is not clear, but resistance to PTH may play a role. Hypocalcemia is usually asymptomatic, due to counterbalancing effect of acidosis: decreased pH results in increased Ca ions and decreases muscular excitability
8. Metabolic acidosis
   It is a daily production of approximately 1 mmol/kg of body weight of nonvolatil acid from endogenous metabolic surces. They are not eliminated by the abnormal kidney and the injured tubules are not able to reabsorb bicarbonate.
9. Hematologic abnormalities
   - normocytic normochromic anemia, due to impaired erythropoesis, shortened red blood cell survival, hemodilution, gastrointestinal blood loss
   - leukocytosis: persisting after the initial week of ARF suggest the posibility of infection
   - mild degree of thrombocitopenia, due to impaired bone marrow production and defect in platelet function. They are associated with tendency to bleeding.
10. Cardiovascular complications include:
    - volume overload, due to excessive water and sodium administration without excretion

- mild hypertension is a manifestation of extracellular fluid volume overload and of increased activity of renin-angiotensin-aldosteron system
- cardiac arrhythmias, due to congestive heart failure, electrolyte abnormalities, anemia
- pericarditis

11. Neurologic abnormalities (agitation, confusion, generalized seizures) due to uremia and metabolic and electrilyte disturbances
12. Gastrointestinal complications

Ureea is eliminated through the gastrointestinal wall and it is transformed into ammonia. It is responsable for gastritis, vomiting, gastro-intestinal hemorrhages

The recovery phase commence when the GFR increses so that the blood urea nytrogen and serum creatinine concentration begins to decrease and urine volume increases. But, persistent abnormalities of glomerular and tubular function (loss of concentrating ability), can elad to over or underhydration or electrolyte disturbances.

Although the major improvement in renal function occurs within 102 weeks, renal function continues to improve for up to a year following acute renal failure.

II.4.5. Pathophysiology of chronic renal failure

It is a clinical condition resulting from a progressive pathologic process that lead to severe and progressive decrease of renal excretory function. it is caused by the irreversible reduction of the functional nephron mass.

Etiology:

- chronic renal diseases (chronic primary or secondary glomerulopathies, tubulo-interstitial kidney diseases)
- tuberculosis of the kidney
- nephrolithiasis with its complications
- congenital causes: polycystic kidney disease

Reduction of the renal mass causes structural and functional hypertrophy of the remaining nephrons. A fundamental feature of this intact nephron hypothesis is that following of nephron mass, renal function is due primarily to the surviving healthy nephrons, while the damaged nephrons cease functioning. There are a compensatory hypertrophy and it is due to adaptative hyperfiltration mediated by increases in glomerular capillary blood volume and tubular function.

1. Effect of reduced nephron mass on sodium chlorid transport in the surviving nephrons.

The compensatory hypertrophy refears as the blood flow, GFR and transport function increase above normal value in remaining nephrons. with progressive destruction of nephrons, maintaenance of external balance of NaCl(ingested Na – excreted Na) requires that salt excretion increase as GFR decreases. It is an adaptative increase in salt excretion per nehpron. Several mechanisms contribute to this phenomena:

- probably a rise in peritubular capillary hydrostatic pressure inhibit proximal tubular reabsorbtion
- when GFR is decreased, ureea , creatinine and organic acidsaccumulate in the blood. These substances are excretesd by filtration and tubule secretion. When plasma level of these substances are increased, sufficient fluid may accompany this secretion into the proximal tubule by osmosis to diminish net fluid reabsorbtion.
- atrial natriuretic peptide inhibits the Na tubular reabsorbtion in the

2. Effect of reduced nephron mass on water reabsorbtion.

With reduced nephron mass, there is an increase in excretion of solute per nephron and that obligates a nearly isoosmotic amount of water and solute diuresis appears. So, isostenuria is an universal finding when GFR falls below 25ml/minute, suggesting the concentrating defect of the kidney.

3. Hydrogen and bicarbonate transport

The maintaining of a normal pH of extracellularfluid is very important ot survival. Metabolic surces determines 1 mmol hydrogen ion per kg of body weight per day. The kidney prevent the possibility of acidosis by the following processes:

- regenerating of bicarbonate
- reabsorbtion all the filtrated bicarbonate in the proximal tubule
- excretion of the hydrogen ions by ammoniogenesis or bound to phosphate (the titrable acids)

Progressive loss of renal function causes no change in arterial pH until GFR falls below 50% of normal. But, when GFR is decreased more, metabolic acidosis appears.

Acidosis has two mechanisms: glomerular (retention of anions- sulfates and phosphates) and tubular (retention of bicarbonate and excretion of protons are reduced)

4. Effect of reduced nephronal mass on tubular potasium transport

Filtered K is reabsorbed in the tubule and then K is secreted into the distal tubule. This secretion is increased in CRF depending on:

- the aldosteron level
- increased luminal electronegativity, created by the concentration of anions

In CRF, as GFR declines, the tubules facilitate the excretion of greater fractions of the filtered load of K, either by enhancing net secretion and by diminishing net reabsorbtion. Thus, excretion rate per nephron and fractional excretion increase. For

K, increased fractional excretion serves to maintain normal plasma level until GFR falls to less one-fourth of normal.

The severity of CRF often vary greatly depending on the magnitude of the reduction in functioning renal mass. There are four stages of CRF:

1. *Early stage,* in which GRF is reduced to a levels about 35-50% of normal. At this stage, the patient is symptom-free and the renal function are generally well maintained.

2. *Later stage,* in which GFR is about 25-35% of normal.

The patient is asymptomatic because there are any compensatory mechanisms:

- hypertrophy of surviving nephrons
- poliuria with hypostenuria, due to solute diuresis and the presence of tubulo-glomerular balance (the tubular function exists in direction that serve to supress tubular reabsorbtion of water and Na)

Azotemia appears in any sudden stress (infections , dehydration), because of the decompensation of the damaged kidney.

3.*Overt renal failure,* in which GFR is below 20-25% of normal

4. *Final sateg, called uremic state*

It is a term applied to the clinical syndrom determined by retention in the blood of ureea and other end products of metabolism.

Clinical course and laboratory findings of CRF

1. Na and water homeostasis

Generally, patients with CRF have impaired renal mechanisms for concerving Na and water. When an extrarenal cause for fluid loss is present (vomiting, diarrhea), extracellular fluid depletion occurs, with signs of dry mouth, dizziness, tachycardia, orthoatatic hypotension and vascular collapse. Depletion of extracellular fluid results in deterioration of residual renal function and uremic stage may appears suddenly. Hyponatremia is a a frequent future of CRF, caused by diuretic therapy, extrarenal loss, decreased salt ingestion. Hemodilution also causes hyponatremia but increases of extracellular fluid exists usually in the late stages and edema appears.

2. Potasium homeostasis

Despite of progression of renal failure, most patients maintain normal serum potasium concentrations because of the adaptation mechanisms of the secretory function of the tubule.

Hyperkalemia is caused by :

- decreased of ultrafiltrated K , when GFR are of very low level
- metabolic acidosis is associated with the reciprocal changes between H and K, with efflux of K from intracellular fluid to extracellular space.

- hyporeninemic hypoaldosteronism, especially in CRF due to diabetic nephropathy
- endogenous hemolysis or trauma
- exogenous: infusion of stored blood or administration of K-containing medication

Hypokalemia is due to :

- gastrointestinal loss
- poor dietary K intake
- excessive diuretic therapy
- CRF is secondary to hereditary or acquired tubular transport abnormalities (Fanconi syndrom or renal tubular acidosis)

3. Metabolic acidosis due to inability of the kidney to maintain acid-base balance: with advancing CRF, total daily acid excretion and buffer production fall below the level needed to maintain external balance of hydrogen ions.

4. Phosphate, calcium and bone

Hypocalcemia is a common future in CRF due to:

- the impaired ability of the kidney to synthesize 1,25(OH)2-vitamine D, the active metabolite of vitamine D, and decreased intestinal reabsorbtion of calcium
- serum phosphate concentration is increased with deposit of Ca in the bone, if calcium-phosphate product is more than 60.

In early stage, hypocalcemia causes an increased level of PTH (secondary hyperparathyroidism) which tends to eliminate the calcium from the bone. But, later the bone becomes resistent to PTH and the ability of PTH to mobilize calcium salts from bone may by altered. Renal and metabolic *osteodistrophy* is a term that encompass a number of skeletal abnormalities including:

- osteomalacia and osteoporosis because of decreaesd responsivenes of bone to 1,25(OH)2, D3 , protein-caloric malnutrition, metabolic acidosis with dissolution of bone buffers
- renal rickets: impaired of bone growth in children, due to protein defficiency and hypocalcemia
- osteosclerosis and osteitis fibrosa cystica are acused by the increased PTH secretion and remodeling of the bone
- metastatic calcification (subcutaneous, articular, myocardium), if the calcium- phosphate products are very high

5. cardiovascular and pulmonary abnormalities

- fluid retention results in congestive heart failure or pulmonary edema.There is a low pressure pulmonary edema due to either increased

hydrostatic pressure and increased peremability of alveolar capillary membrane.

- arterial hypertension is the most common complication of the end stage of renal disease.
- pericarditis is due to retained metabolic toxins other than ureea and creatinine.
- accelerated atherosclerosis because of hypertension, hyperlipidemia, glucose intolerance, metastatic vascular and myocardial calcifications.

6. Hematologic abnormalities
   - normochromic, normocytic anemia, due to:
     - depressed erythropoesis (diminished synthesis of erythropoetin and effect of retained toxins on bone marrow)
     - fibrosis of the bone marrow due to hyperthyroidism
     - hemolysis due to extracorpuscular defects
     - gastrointestinal hemorrhages
     - blood loss is exaggerated in hemodialysis because of the need of heparin
   - abnormal hemostasis characterized by a tendency to abnormal bleeding; decreased platelet aggregation and deficiency of factor 3 activity corelates with increased plasma level of guanidino succinic acid
   - altered defensive responses to infection because of acidosis , protein malnutrition, atrohpy of the lymphoid organs, decreased of ATP-dependent leukocyte functions (chemotaxis, phagocytosis) ; there is a tendency for uremic patients to have less fever in response to infections because of lack of thermogenesis abilities.
7. Neuromuscular abnormalities expressed as :
   - peripheral neuropathy, due to retention of uremic toxins and electrolytic disturbances; usually, sensory nerve involvement exceeds motor (ie, *restless legs syndrome*: sensation of disconfort in the feet and frequent leg movements)
   - dialysis dementia appears at the dialysised patients due to aluminium intoxicaiton
   - headache, seizure, inability to concentrate are atribuated to acidosis and to reduced osmolarity of the extracellular fluid leading to cerebral edema and raised intracranial pressure
8. Gastro intestinal abnormalities
   - uremic fetor: uriniferous odour to the breath derives from the breakdown of urea in saliva to ammonia

   - uremic gastroenteritis: mucosal ulceration leading to blood loss due to excretion of urea through the gastrointestinal wall
9. Endocrine-metabolic disturbances:
   - hyperlipoproteinemia, especially high level of triglycerides
   - glucose intolerance (azotemic diabetes0
   - growth and sexual amturation are impaired in children
10. Dermatologic abnormalities
   - pallor, hematomas, pruritus caused by calcium deposition, dehydration
   - yellow color of the skin si due to a combinated influence of anemia and retention of a variety of pigmenteted metabolits (urochromes)
   - uremic frost: urea concentraiton in sweat is very high and after evaporaion of water a fine white powder can be found on the skin
   - uremic pruritus

Pathophysiology and biochemistry of uremic state

Uremia is a term applied to the clinical syndrom caused by the very severe loss of renal function. Although the causes of this syndrom remain unknown, it refers as the changes due to the retention in the blood of the end product of metabolism normally excreted in the urine.

1. The role of retained toxic metabolits

Toxic substances in uremic state are the products of protein and aminoacid metabolism:

- ureea represents some 80% of the total nitrogen excreted in the urine
- the guanidino compounds include guanidine, creatine, creatinine and guanidino succinic acid
- urates and other end products of nucleic acid metabolism
- aliphatic amines
- derivates of the aromatic aminoacids: tryptophan, tyrosine and phenylalanine

Urea may be responsible for anorexia, malaise, vomiting and headache. Guanidinosuccinic compounds interfer with activation of platelet factor 3 by ADP. Creatinine amy cause adverse effects following conversion to more toxic metabolites such as sarcosine and methilguanidine.

- nitrogenous compounds of large molecular weight are also retained and they are responsible for neuropathy

- plasma polypeptide hormons (PTH, glucagon, growth hormon, insulin) are increased in blood because both of impaired renal actabolism and decreased renal excretion. PTh is considered an uremic toxin.

2. Effects of uremia on cellular functions

In uremic states is a decreased activity fo Na-K stimulated ATP-ase. The mechanism remains unknown, probably uremic toxins. This enzyme determines the transport of Na from the cell interior to exterior. The consequences of this eflux are:

- the generation of a resting electrical potential difference across the cell membrane
- the enhanced influx of K into the cell

In CRF, a partial inhibition of this active efflux of Na leads to abnormally high intracellular Na concentration, hyperhydration of the cell, intracellular defficiency of K and reduction in magnitude of transmembrane potential.

CRF is associated with high intracellular concentration of Na and hyponatremia. The same cells are defficient in K and hyperkalemia appears; as a compensatory mechanism, colon secretion of K is increased, due to aldosteron .

3. Effects of uremia on metabolism

- hypothermia: the reduction in basal heat production is due to inhibition of the Na –K pump by some retained toxins.
- carbohydrate metabolism: azotemic pseudodiabetes is associated with peripheral resistance to insulin. The glucose intolerance results from:
  - the rate of cellular glucose utilisation is diminished, leading to glucose intolerance
  - intracellular deficit of K
  - metabolic acidosis
  - high level of glucagon

In insulin-dependent diabetic patients, there is a decreased in insulin requirement with progressive azotemia, because the renal catabolism of insulin is decreased.

- nitrogen metabolism: protein intolerance, due to inability of the kidney to excrete the excess of protein end products.
- lipid metabolism leading to premature atherosclerosis: high level of TG because of decreased catabolism secondary to diminished activity of lipoproteinlipase.

II. 5. Pathophysiology of blood disorders

II.5.1. PATHOPHYSIOLOGY OF RED BLOOD CELLS

1. ESSENTIAL DATA ABOUT ERYTHROCYTES AND ERYTHROPOIESIS

A. Description of erythrocytes. Mature RBC, nonnucleated, biconcave disks, able to pass through very small capillaries, contain hemoglobin, which carries essential gases to and from the tissues.

B. Development: 1.In the **bone marrow** after infancy.
2.Maturation process is from stem cell to mature erythrocyte.
3.**Reticulocyte** - nonnucleated immature cell which remains in marrow one day and then in the blood stream one day before becoming a mature cell.
4. **Reticulocytosis** - increase in peripheral reticulocyte count over 80.000/mm^3 suggests attempt of bone marrow to compensate mature RBC loss.

C. Destruction: 1.Old red blood cells are destroyed by spleen, liver and bone marrow.
2. Iron released from hem is transported by **transferrin** to the bone marrow for red cell production, stored in the form of **ferritin** and **hemosiderin** in the liver and reticulo-endothelial cells.
3. Hem is converted to **bilirubin** which is uptaken by the liver, conjugated and released into the bile canaliculi.

C. Hemoglobin: A protein which contains iron and red pigment
Function: to transport O2 from lungs to tissues and CO2 in the reverse direction.

D. Substances needed for erythropoiesis: amino acids, vitamin B12, folic acid, iron etc.

- **Vitamin B12**: essential for the synthesis of DNA molecules in the immature RBCs. Vitamin B12 must be bound to an **intrinsic factor** for its absorption and is stored in the **liver**.
- **Folic acid** is necessary for the synthesis of DNA and promotes maturation of RBCs.
- **Iron**: essential for production of hem molecule. Iron is absorbed in the duodenum by **transferrin** and stored in the liver as **ferritin**.

E. Energy production in erythrocytes:

- Mitochondria are absent.

- Glucose is virtually the only fuel utilized.
- Glycolisis and the hexose monophosphate shunt are the main metabolic pathways in the red cell.

F. Factors influencing erythropoiesis: - a negative feed-back with **hipoxemia** as stimulus for the release of **erythropoietin** hormone from the kidney.

The red blood cells are all derived from a pool of **pluripotential stem cells**, which gives rise to two distinct types of multipotential stem cells: (1) **hematopoietic stem cells**, which remain in the bone marrow, and (2) **lymphopoietic stem cells**, which migrate to the lymphoid organs.

The hematopoietic stem cell differentiate into three committed **progenitor cell lines** (1) erythroid, (2) granulocytic-monocytic, and (3) megakaryocytic.

Stimulated and regulated by various growth factors, the progenitor cells proliferate and undergo further differentiation to morphologically distinctive **precursor cells** and, in turn, to mature circulating blood cells.

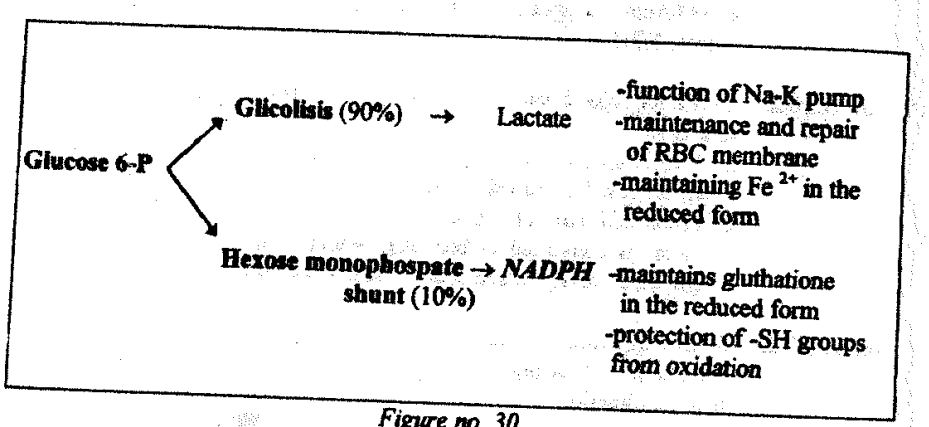
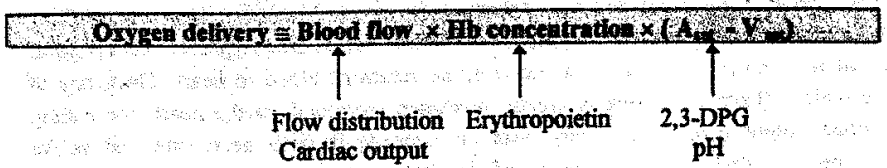


Figure no. 30
The principal metabolic pathways of erythrocytes and their use

Characteristics of hemoglobin

- efficient unloading of oxygen at relatively high oxygen tension is possible because of
- sigmoid shape of the oxygen dissociation curve
- the affinity of hemoglobin for O2 is modified by 4 intracellular factors: **pH, CO_2, 2,3-DPG, temperature**
- increasing the concentration of each of these 4 effectors results in a **"shift to right"** in the oxygen dissociation curve



Oxygen delivery to an organ or tissue is directly proportional to:
1. Blood flow
2. Hb concentration
3. The difference in oxygen saturation of the arterial and venous blood

Compensatory mechanisms in anemia:

- Enhanced blood flow or redistribution
- Decreased O2 affinity by increased levels of 2,3 -DPG
- If the patient has a defective Hb variant with increased oxygen affinity erythropoietin secretion is stimulated and an increased number of red cells is produced.

2. ANEMIAS

Definition: Anemia is a condition in which there is a reduction in the number of circulating RBCs, or in hemoglobin concentration or in the volume of packed red cells (hematocrit), or a combination of these factors.

Clinical features

Depends on the **severity**, the **time of development** and the **underlying disease**.

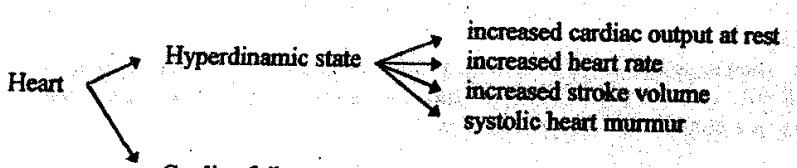
- A mild to moderate anemia may not produce clinical consequences if there isn't any associated pathology but may unmask local vascular diseases (e.g. coronary insufficiency). With hemoglobin levels below 7g/dl signs and symptoms related to decrease oxygen supply and decreased blood flow to certain territories become manifest. The blood is shunted away from the skin and peripheral tissues to enhance the oxygen supply to vital organs.
- The clinical symptoms also depend on the rapidity of the onset of the anemia. For example, acute blood loss due to a massive hemorrhage may precipitate shock. By contrast, the insidious development of an anemia of comparable severity is well tolerated because of compensatory increase in plasma volume and cardiac output. In addition, there is a decrease in the oxygen affinity of hemoglobin caused by an increase in erythrocyte 2,3-diphosphoglycerate content which determines a shift to right of the hemoglobin dissociation curve.

Effects of the anemia on the circulatory system

The viscosity of the blood depends almost entirely on the concentration of the red blood cells. In severe anemia, the blood viscosity may fall to as low as 1.5 times that of water rather than the normal value of about 3. This decreases the resistance to

the blood flow in the peripheral vessels so that far greater than normal quantities of blood flow to the tissue and than return to the heart. Moreover, hypoxia resulting from diminished transport of oxygen by the blood causes the peripheral tissue vessels to dilate, allowing still further increase in the return of blood to heart. Thus, one of the major effects of anemia is greatly increased workload on the heart: the resting cardiac output rises significantly with an increase in both heart rate and stroke volume. The patient may be aware of this **hyperdinamic state** and complains of palpitation or a pounding pulse.

The increased cardiac output in anemia partially offsets many of the effects of the anemia because even though each unit quantity of blood carries only small quantities of oxygen, the rate of blood flow may be increased enough so that almost normal quantities of oxygen are delivered to the tissues. However, when a person with anemia begins to exercise, the heart is not capable of pumping much greater quantities of blood than it is already pumping. Consequently, during exercise, which greatly increases the tissue demand for oxygen, extreme tissue hypoxia results and acute cardiac failure often ensues.



Nonspecific signs and symptoms:

- Central nervous system: dizziness, headache, syncope, vertigo, irritability
- Skin: pallor, hypersensitivity to cold
- Gastrointestinal symptoms: anorexia, indigestion, and even nausea or bowel irregularity
- Genital symptoms: impotence, loss of libido, abnormal menstruation

Specific signs:

- **Koilonychia**: spoon-shaped nails seen in iron deficient anemia
- **Jaundice**: found in hemolytic anemia
- **Bone deformities**: found in thalassemia major
- **Leg ulcers**: in sickle cell disease, etc.

CLASSIFICATION OF ANEMIA ACCORDING TO UNDERLYING MECHANISM

I. Impaired red cell production

- **A. Stem cell disorders**: Aplastic anemia, Myelophthisic anemias due to marrow infiltration, Myelodisplasia
- **B. Progenitor cell disorders**: Pure red cell aplasia, Chronic renal failure, Chronic disease, Sideroblastic anemia
- **C. Precursor cell disorders (erythroblasts):**
  - 1.Defective DNA synthesis: Deficiency or impaired utilization of vitamin B_{12} and folic acid (megaloblastic anemias)
  - 2. Defective hemoglobin synthesis
    - a. Deficient hem synthesis: Iron deficiency
    - b. Deficient globin synthesis: Thalassemias

II. Increased rate of destruction (Hemolytic anemias)

- **A. Intrinsic (intracorpuscular) abnormalities of red cells**
  - 1. Red cell membrane disorders: Spherocytosis, elliptocytosis
  - 2. Red cell enzyme deficiencies : G6PD deficiency
  - 3. Disorders of hemoglobin synthesis
    - a. Deficient globin synthesis: Thallassemia syndromes
    - b. Structurally abnormal globin synthesis: Sickle cell anemia
- **B. Extrinsic (extracorpuscular) abnormalities**
  - 1. Antibody-mediated
    - a. Isohemagglutinins: Transfusion reactions, erythroblastosis fetalis
    - b. Autoantibodies: Idiopathic (primary), drug-associated, SLE, malignancies, mycoplasma infection
  - 2. Mechanical trauma to red cells
    - a. Microangiopathic hemolytic anemias: Thrombotic thrombocytopenic purpura, DIC
    - b. Cardiac traumatic hemolytic anemia
  - 3. Infections: Malaria
  - 4. Chemical injury: Lead poisoning
  - 5. Sequestration in mononuclear phagocyte system: Hypersplenism
- **C. Acute blood loss**

Classification of anemias according to morphology of RBCs

- **A. Normocytic, normochromic**: Hemolytic anemias, Acute blood loss
- **B. Microcytic, hipochromic**: Iron deficiency, Thalassemias
- **C. Macrocytic**: Megaloblastic anemias - Vitamin B_{12} and folic acid deficiency

2. I.A.1. APLASTIC ANEMIA

Aplastic anemia is a chronic disorder of hematopoietic stem cells that results in the cellular depletion of the bone marrow and pancytopenia.

Pathogenesis: In some patients there is an initiating event such exposure to certain drugs, toxins, and viruses. In most cases, however, no cause is found, such situation being termed **idiopathic**. It is believed that the primary lesion involves an inability of stem cells to regenerate and repopulate the marrow. The successful therapeutic use of anti-T-lymphocyte antibodies and other immunosuppressive agents

for the treatment of aplastic anemia suggests that there is an immunologic component either in the pathogenesis of the disease or in its subsequent progression. The peripheral blood invariably exhibits pancytopenia.

2. I.B.1. ANEMIA ASOCIATED WITH CHRONIC DISEASE

Anemia associated with chronic disease is one of the most common anemias worldwide, second only to iron deficiency mild to moderate **normochromic or hypochromic anemia**, with a hemoglobin level of **9 to 11 g/dl**, is frequent in:

- chronic inflammatory disorders (e.g. rheumatoid arthritis and systemic lupus erythematosus)
- chronic infectious diseases (e.g. tuberculosis and AIDS)
- cancer

Fortunately, it is not severe enough to cause major symptoms, but it may render the underlying disorders more difficult to endure.

There is:

- a decreased iron supply to the developing erythroblasts and
- a slightly shortened erythrocyte life span.
- an impaired bone marrow response to erythropoietin
- an inadequate production of erythropoietin in the response to anemia.

The basis of this defect is not clear but increased secretion of cytokines , as interleukin-1 has been implicated.

The presence of increased iron storages in the bone marrow macrophages, a high serum ferritin level, and reduced total iron-binding capacity rule out iron deficiency as a cause of a hypochromic anemia.

2. I. B.2. ANEMIA OF CHRONIC RENAL DISEASE

A mild normocytic, normochromic anemia is commonly observed in association with chronic renal disease. Erythrocytes with reguiarly scalloped margins (bur cells) are characteristic. The severity of the anemia is related to the degree of anemia. The causes of the anemia reflect both a decreased rate of erythrocyte production and an accelerated peripheral loss of erythrocytes. The most probable causes are:

- Decreased production of erythropoietin by the damaged kidneys
- Hemorrhagic diathesis due to qualitative defects in the platelet function or to abnormalities in vascular integrity produced by uremia.
- Decreased life span of erythrocyte by unknown mechanism
- Iron deficiency due to blood loss

2. I.B.3. SIDEROBLASTIC ANEMIAS

These comprise a group of disorders of diverse causes characterized by **ringed syderoblasts** in the nucleated erythroid precursors in the bone marrow. There is an

associated mild to moderate anemia because of the premature destruction of abnormally maturing erythroid cells in the bone marrow.

In the mitochondria of normally developing erythroblasts, iron is inserted into protoporphyrin to form hem. In the cytosol, hem then combines with globin to form hemoglobin. When hem production is impaired, iron in the form of ferritin accumulates in the mitochondria, causing damage to and even rupture of these organelles. In the developing normoblast, the mitochondria are situated in a perinuclear location. In sideroblastic anemia, the Prussian blue stain demonstrates the iron-laden mitochondria as a granular blue ring that encircles the nucleus.

Sideroblastic anemia may occur as a :

- Hereditary disorder
- Secondary finding in a variety of hematologic, inflammatory, and neoplastic diseases
- Result of exposing to bone marrow toxins
- Idiopathic acquired disorder

Laboratory examination:

Peripheral blood:

- Mild to moderate hypochromic microcytic anemia reflecting impaired hem synthesis
- A marked increase in serum iron and transferin saturation

Bone marrow:

- Erythroid hyperplasia with decreased red cell production (ineffective erythropoiesis)
- > 10% ringed sideroblasts

2. I.C.1. MEGALOBLASTIC ANEMIAS

- The erythroid precursors and erythrocytes are abnormally large because of the impairment of cell maturation and division owing to a deficiency of either vitamin B12 or folic acid.
- Vitamin B12 and folic acid are coenzymes of DNA synthetic pathway.
- The synthesis of RNA and proteins is unaffected.
- There is an asyncronism between the cytopiasm and nuclear maturation.

Pernicious anemia:

Cause of vitamin B12 malabsorption: atrophic gastritis with failure of production of intrinsic factors.

Table 24 - Causes of megaloblastic anemias

VITAMIN B_{12} DEFICIENCY	
Decreased intake	Inadequate diet
	Impaired absorption
	Intrinsic factor deficiency
	• Pernicious anemia
	• Gastrectomy
	Malabsorption states
	Diffuse intestinal disease-e.g. lymphoma, systemic sclerosis
	Ileal resection, ileitis
	Competitive parasitic uptake
	Bacterial overgrowth in blind loops and diverticula of the bowels
Increased requirement	Pregnancy, hyperthyroidism, disseminated cancer
FOLIC ACID DEFICIENCY	
Decreased intake	Inadequate diet- alcoholism, infancy
	Impaired absorption
	Malabsorption states
	Intrinsic intestinal disease
Increased requirement	Pregnancy, infancy, disseminated cancer
Impaired utilization	Folic acid antagonists

Biochemical functions of vitamin B_{12}:

- **N5- methyltetrahydrofolate - homocysteine methyltransferase** involved in the conversion of homocystheine to methionine. In this reaction N5- methyl-tetrahydrofolic acid (N5-methyl-FH4), the principal form of folic acid in plasma, is converted to tetrahydrofolic acid (FH4). The FH4 is required for the conversion of deoxyuridine monophosphate (dUMP) to deoxythimidine monophosphate (dTMP), which is an immediate precursor of DNA.

It has been postulated that the fundamental cause of impaired DNA synthesis is the reduced availability of tetrahydropholic acid, since most of it is trapped as N5-methyl-FH4. Because the methylated form cannot be converted directly to other forms of tetrahydrofolate, the N5- methyl form accumulates, whereas the levels of the other forms decrease. Thus, cobalamin deficiency is hypothesized to lead to a deficiency of the tetrahydrofolate forms needed in purine and thymine synthesis,

resulting in the symptoms of megaloblastic anemia. This theory is supported by the observation that the anemia improves with the administration of folic acid.

- **Methylmalonyl-CoA mutase** involved in the isomerization of methylmalonil-CoA to succinil-CoA in the pathway of the oxidation of fatty acids with an odd number of carbons. Vitamin B12 deficiency could lead to the accumulation of abnormal fatty acids that may be incorporated into neuronal lipids. This biochemical abnormality may predispose to myelin breakdown and thereby produce some of the neurological complications of vitamin B12 deficiency. The administration of folic acid fail to improve the neurologic deficit.

Pathogenesis: Pernicious anemia is believed to result from immunologically mediated destruction of gastric mucosa resulting in **chronic atrophic gastritis.** Autoantibodies against intrinsic factor (IF) or parietal cells are raised with marked loss of parietal cells. Since the absorption of vitamin B12 requires the intrinsic factor which is secreted by the parietal cells a deficiency in vitamin B12 will develop.

Types of cell affected:

- cells with increased turn-over (mythosis are frequent and requires large quantities of DNA to be produced):
  1. cells of alimentary tract: especially tongue and stomach
  2. bone marrow cells
- neurons

Morphology

Peripheral blood

- erythrocytes are macrocytic: MCV > 100 fL
- MCHC is not elevated
- neuthrophils are larger than normal and hypersegmented

Bone marrow:

- hypercellularity
- megaloblastic change in all stages of red cell development
- granulocytic precursors and megakaryocytes are also abnormally large
- the erythroid-to-myeloid ratio, normally 1:3, may be transformed to 1:1

There are two pathologic processes which contribute to the development of anemia:
(1)**ineffective erythropoiesis** - intramedullary destruction of megaloblasts
(2)**increased hemolytic destruction**

Gastric mucosa:

- Parietal cells are almost absent. **Achlorhydria** is the consequence of gastric atrophy. The atrophic gastritis does not recover after vitamin B12 replacement.

- Glandular epithelium are replaced by mucus secreting goblet-cells a process called intestinalization. These cytological aberration in the gastric mucosa are associated with an increased risk of gastric cancer.

Central nervous system lesion involves the spinal cord, where there is myelin degeneration of the dorsal and lateral tracts.

2. I.C.2. IRON DEFICIENCY ANEMIA

Iron deficiency is the most common cause of anemia and may result from (1) dietary lack, (2) impaired absorption, (3) increased requirement, (4) or chronic blood loss.

Iron requirements are best understood in the terms of the fixed daily losses of iron, ranging between 1 and 1.5 mg. Thus to maintain a normal iron balance approximately 1 mg of iron must be absorbed from the diet every day. Because only 10 to 15% of the ingested iron is absorbed, the daily iron requirement for adult males is 5 to 10 mg and for adult females 7 to 20 mg. Since the average daily intake of iron is about 15 to 20 mg, most men ingest more than adequate iron, whereas many women consume just enough or marginally adequate amounts of iron.

Dietary lack is a rare cause of iron deficiency in industrial countries having abundant food supplies (including meat) and where about two thirds of the dietary iron is in the readily assimilable hem form. The situation is different in the developing countries, where food is less abundant and diets are predominantly vegetarian, containing poorly absorbable inorganic iron.

Infants are also at high risk because the diet, predominantly milk, contains very small amounts of iron.

Impaired absorption is encountered in sprue, other causes of intestinal steatorrhea, and chronic diarrhea. Gastrectomy impairs iron absorption by decreasing hydrochloric acid and transit time through the duodenum.

Increased requirements are common in growing infants and children, adolescents, and pregnant women which are at particular risk for developing iron deficiency.

Chronic blood loss is by far the most common cause of iron deficiency in adults. *It should be considered to be caused by gastrointestinal blood loss until proven otherwise. To prematurely ascribe an iron lack in such individuals to any of other possible origins is to run the risk of missing an occult gastrointestinal cancer or other bleeding lesion (e.g. peptic ulcer).*

Iron deficiency induces a hypochromic microcytic anemia.

Cell growth and proliferation are impaired by iron deficiency. After the cells of the bone marrow, those of the *gastrointestinal tract* have the highest proliferative

activity. Consequently many of the signs and symptoms of iron deficiency are localized to this organ system: glossitis, angular stomatitis and, occasionally, gastric atrophy with achlorhydria and intestinal malabsorption. Depletion of iron containing enzymes throughout the body may cause other changes, including koilonychia and alopecia.

Uncommonly, esophageal webs may appear, to complete the triad of major findings in the **Plummer-Vinson syndrome**: (1) microcytic hypochromic anemia, (2) atrophic glossitis, and (3) esophageal webs.

Laboratory examination:

Peripheral blood:

- Red cells appear smaller (**microcytic**) and much paler (**hypochromic**) than normal.
- In many cells hemoglobin may be seen only in the form of a narrow peripheral rim (**anulocytes**).

The serum iron and serum ferritin are low, and the total plasma iron binding capacity (reflecting transferrin concentration) is high.

Bone marrow:

- Increased erythropoietic activity with increased number of erythroblasts.

Disappearance of stainable iron from the reticuloendothelial cells.

2. II. HEMOLYTIC ANEMIAS

General characteristics:

1. shortening of the normal red cell life span
2. accumulation of the products of the hemoglobin catabolism
3. marked increase in erythropoiesis within bone marrow in an attempt to compensate for the loss of red cells

Clinical presentation: splenomegaly, jaundice, fever, dark urine, dark stools

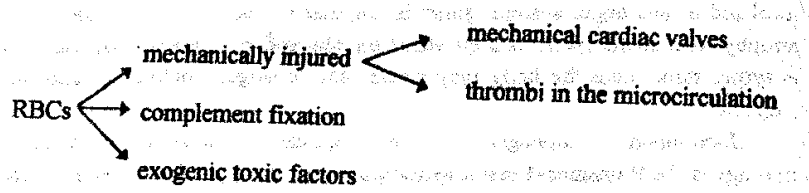
Premature destruction of the red cells could be **extravascular** or **intravascular**.

Extravascular hemolysis:

The red cells become less deformable or are rendered foreign being sequestered into the splenic cords.

RBCs
- rendered foreign - has surface bound Ig - **Immunohemolytic anemias**
- less deformable
  - ↓ viscoelastic properties of RBCs membrane
  - ↓ ratio of surface area to volume: **spherocytosis**
  - intracellular aggregates of Hb into RBCs
    - polymers - **sickle cell disease**
    - precipitates - **thalassemias, Heinz bodies anemias**

Intravascular hemolysis:



When hemoglobin escapes into the plasma, it is promptly bound by an α2 globulin (**haptoglobin**) to produce a complex which is cleared by the reticuloendothelial system. A decrease in the serum haptoglobin level is characteristically seen in all cases of intravascular hemolysis.

When the haptoglobin is depleted, the unbound free hemoglobin is excreted through the kidneys - **hemoglobinuria**.

Within the tubular cells, iron released from the hemoglobin produces hemosiderosis of the renal tubular epithelium - shedding of these cells into the urine constitutes **hemosiderinuria**.

The hem groups are catabolized within the reticuloendothelial system to **bilirubin** leading to **jaundice**. The serum **bilirubin is unconjugated** and the level of hyperbilirubinemia depends on the capacity of the liver as well as on the rate of hemolysis.

Excessive bilirubin excreted by the liver into the gastrointestinal tract leads to increased formation of **urobilinogen** which is partially absorbed by the intestinal mucosa and is eliminated through the kidneys giving the **dark colour of the urine**, and partially is eliminated with stools as **stercobilinogen (dark stools)**.

Table 25 - Laboratory evaluation of hemolysis

Hematologic	**Extravascular**	**Intravascular**
Routine blood film	Polichromatophilia	Polichromatophilia
Reticulocyte count	↑	↑↑
Bone marrow examination	Erythroid hyperplasia	Erythroid hyperplasia
Plasma or serum		
Bilirubin	↑, Unconjugated	↑, Unconjugated
Haptoglobin	↓	absent
Plasma hemoglobin	-	↑
Methemalbumin	0	+
Urine		
Bilirubin	0	0
Urobilinogen	Increased	Increased
Hemosiderin	0	+
Hemoglobin	0	+

2. II.A.1. HEREDITARY SPHEROCYTOSIS

Pathogenesis:

- autosomal dominant disorder
- deficiency of spectrin (protein of the red cell cytoskeleton)
- reduced membrane stability and spontaneous loss of RBCs membrane
- splenic trapping of RBCs

Clinical features:

- anemia, splenomegaly and jaundice
- splenectomy is usually curative

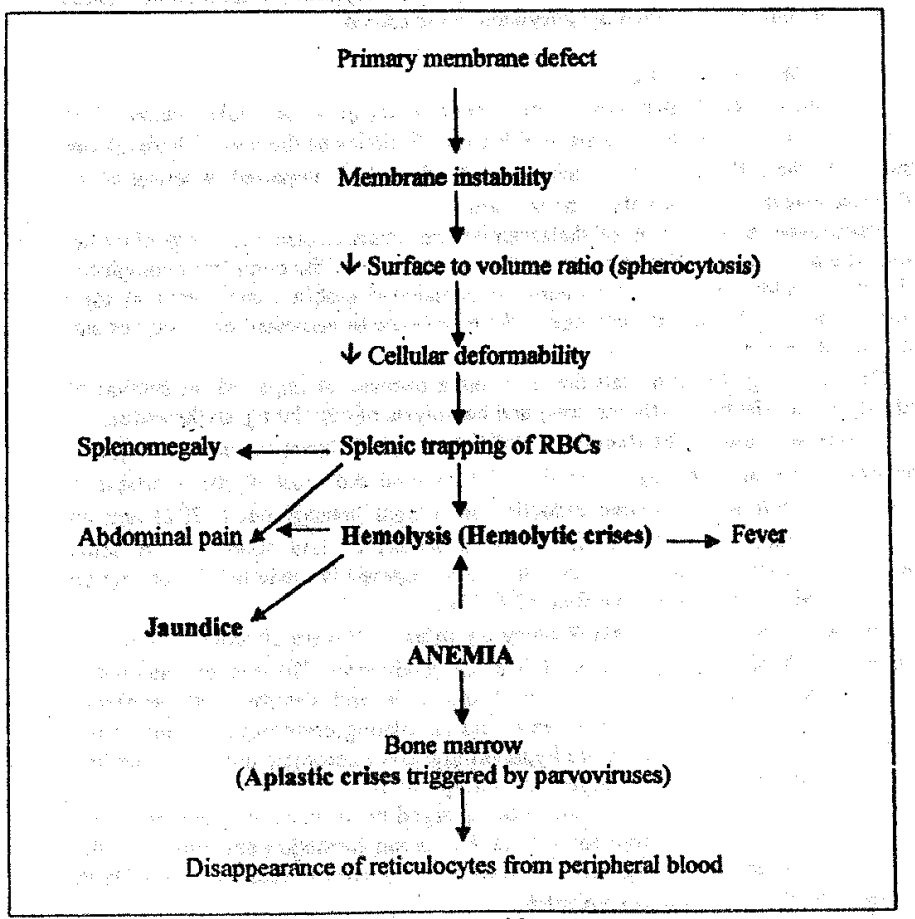


Figure no. 31

Pathogenesis of hereditary spherocytosis

II.A.2. HEMOLYTIC DISEASE DUE TO G6PD DEFECT

Glucose-6-phosphate dehydrogenase (G6PD) deficiency refers to a large group of X-linked, hereditary, hemolytic anemias in which an inadequate activity of erythrocyte G6PD predisposes to episodes of hemolysis precipitated by drugs or infections.

Pathogenesis: G6PD is an enzyme of the hexose monophosphate shunt pathway that maintains glutathione in its reduced (active) form. G6PD reduces NADP to NADPH while oxidizing glucose-6-phosphate. NADPH then provides the reducing power that converts oxidized glutathione to reduced glutathione. Normally, intracellular reduced glutathione inactivates the oxidants which might injure the red cell. Erythrocytes that are deficient in G6PD are less resistant to oxidation caused by **infections** or by **exposure to oxidant drugs**. Under such stress, hemoglobin is denatured and precipitates as **Heinz bodies** on the erythrocyte membrane. These abnormal erythrocytes are then phagocytized in the spleen.

2. II.A.3н. THALASSEMIA

Thalassemia syndromes are a heterogeneous group of heritable anemias that have in common defective synthesis of either α or β chains of the normal hemoglobin tetramer. In the β-thalassemias, synthesis of the β chain is impaired, whereas in the α-thalassemias the defect involves the α chain.

Pathogenesis: All forms of thalassemias are characterized by a hypochromic, microcytic anemia, owing to reduced or absent synthesis of the complete hemoglobin molecule. In addition, the accumulation of unmatched globin chains leads to their precipitation, with consequent damage to the membrane of nucleated erythrocytes and mature erythrocytes.

Defective β-globin synthesis causes anemia because of impaired production of erythrocytes (ineffective erythropoiesis) and hemolysis of circulating erythrocytes.

In heterozygous β- Thalassemia (β-Thalassemia Minor) the normal β-globin gene usually produces enough β or δ chains to bind the most of the available α chains. The result is a moderate reduction in normal hemoglobin (α2β2) and an increase in hemoglobin A2 (α2δ2). There is usually a mild anemia, with some hypochromia, microcytosis and target cells. The diagnosis is made by demonstration of an increased amount of hemoglobin A2 (>5%).

Homozygous β-Thalassemia (Cooley anemia) is a severe disorder caused by a pronounced reduction in or absence of β chain production. The excess unpaired α chains readily precipitate within the erythroid cells and destroy both erythroid precursors cells (ineffective erythropoiesis) and circulating erythrocytes (hemolysis). The peripheral blood erythrocytes are hypochromic and microcytic and show marked anisocytosis, poikilocytosis, and target cell configuration.

The facial and cranial bones tend to be enlarged or distorted because of severe bone marrow hyperplasia. Extramedullary foci of blood formation are present in the spleen, liver, and paraspinal regions. The spleen is increased in size because of both production and destruction of erythrocytes.

Intensive transfusion therapy has diminished some of the effects of ineffective erythropoiesis and hemolysis in Cooley anemia and iron chelators were used concomitantly to prevent secondary iron overload.

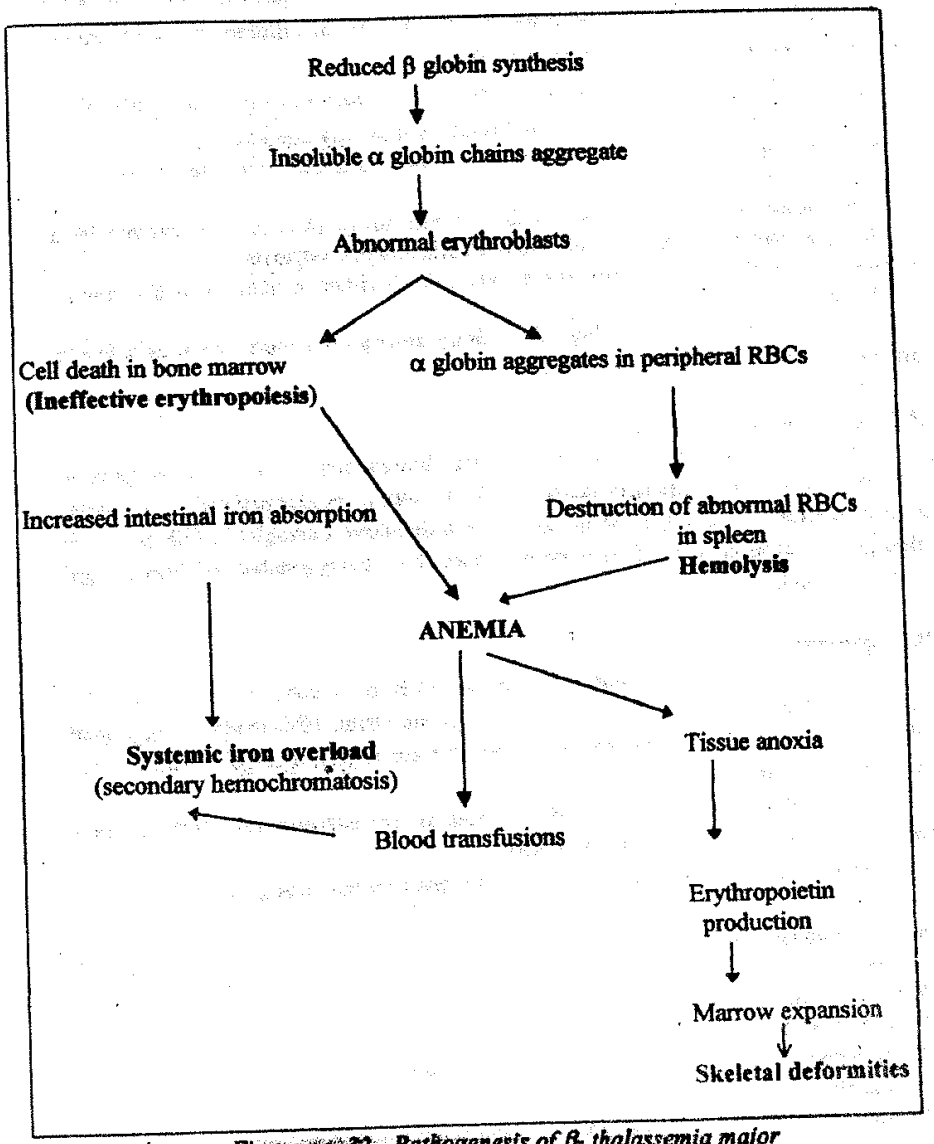


Figure no. 32 - Pathogenesis of β- thalassemia major

α-Thalassemia comprises four distinct syndromes, each of which reflects the failure of one or more of the four α-gene loci on chrosome 16 to function.. In utero and in the neonatal period, impaired synthesis of γ chains causes the precipitation of unmatched γ chains as **hemoglobin Barts (γ4),** whereas in children and adults excess β chains are deposited as **hemoglobin H (β4).**

The severity of the four diseases depends on the number of the chains deleted.

- **The silent carrier** state is caused by the deletion of only one gene
- **α-Thalassemia trait** reflects the deletion of the two genes, which results in only a mild hemolytic anemia.
- **Hemoglobin H disease**, in which three genes are deleted, is characterized by a moderate hemolytic anemia, with hypochromia and microcytosis.
- **Deletion of all four α chain genes** causes death either in utero or at the time of delivery.

The predominance of the high O2 affinity hemoglobin Barts produces a severe impairment of oxygen delivery in utero.

II.A.3b. SICKLE CELL DISEASE

Refers to a group of hereditary hemoglobinopathies in which deoxygenated erythrocytes undergo a transformation from the normal biconcave disk to a sickle-shaped structure. This shape change is due to a defective hemoglobin (Hb S) which undergo aggregation and polymerization when it is deoxygenated to form a rigid filamentous gel.

Pathogenesis:

- HbS is the result of a point mutation that leads to the substitution of valine for glutamic acid at the sixth position of the beta globin chain. HbS tends to aggregate and polymerize at low oxygen tension to form a rigid filamentous gel which renders the erythrocyte rigid and less deformable.

- The predominance of HbS leads to both severe **chronic hemolytic anemia** and to **occlusion of the small blood vessels.**

- Person with sickle cell anemia are homozygous for the HbS gene.

Clinical manifestations:

I. Vasooclusive crises:

1. **Microinfarcts** - painful crisis
2. **Macroinfarcts** - organ damage:

- Autosplenectomy -Increased susceptibility to infections
- Myocardial ischemia
- Pulmonary infarction and infections - Rapidly progressive decrease in pulmonary function - Acute chest syndrome

- Impaired ability to concentrate urine, renal infarcts
- Stroke
- Hemorrhage of retina, proliferative retinopathy
- Leg ulcers

II. Aplastic crises: Intercurrent infections, both viral and bacterial, tend to depress the normal rate of erythrocyte production. Since hemolysis continue unabated, the hemoglobin concentration falls rapidly, a condition called aplastic crises.

III. Sequestration crises: Intercurrent infections may cause hyperplasia of spleen, with sudden pooling of erythrocytes and a rapid fall in the hemoglobin levels. This complication accounts for most of the deaths from sickle cell anemia in the early years of life.

Crises are associated with: **Infection, Dehydration, Acidosis**

II.B.1. AUTOIMMUNE HEMOLYTIC ANEMIAS

Autoimmune hemolytic anemias are caused by autoantibodies with specificity for erythrocyte membrane proteins. They are either **warm reacting** or less commonly **cold reacting**, in which case the activity increases at temperatures below 37°C.

Warm reacting autoantibodies

Represents about 80% of all autoimmune anemias.

It occurs as:

1. an idiopathic disorder
2. in association with a variety of malignant or benign conditions (lymphomas, collagen vascular diseases, inflamatory disorders like ulcerative colitis)
3. as a response to a number of drugs

Pathogenesis:

- Warm antibodies are usually of the IgG class and are often directed at the core antigen of the Rh locus.
- The erythrocytes are mostly destroyed in the splenic sinusoids by macrophages with receptors for the Fc portion of Ig G and C3b component of the complement.
- The Coombs test is positive.

Cold reacting antibodies:

Represents about 20% of cases of immunohemolytic anemia.

This type of hemolytic anemia occurs as a:

1. Idiopathic chronic disorder
2. In elderly persons in whom features of malignant lymphomas subsequently develops
3. In young persons who have acute mycoplasma or Ebstein-Barr infections

Pathogenesis: Cold antibodies are usually of the IgM class and generally have specificity for the I/i antigen complex. When blood is pooled in the extremities, IgM antibodies fix C3 to the erythrocyte membrane. Since IgM subsequently dissociates at 37°C, only complement components are identified on the erythrocyte surface membrane by Coombs test. These complement coated red blood cells are removed principally by hepatic Kupffer cells.

Erythroblastosis fetalis is usually caused by immunization of an Rh negative mother by the erythrocytes of an Rh positive fetus (see picture at the end).

II.B.2. HEMOLYTIC ANEMIA SECONDARY TO MECHANICAL ERYTHROCYTE DESTRUCTION

Microangiopathic hemolysis is caused by the fragmentation of erythrocytes by fibrin strands in partially obstructed small peripheral blood vessels. Disseminated intravascular coagulation is a frequent cause.

Hypersplenism may cause hemolytic anemia associated with leukopenia and thrombocytopenia. This is especially true with congestive splenomegaly as occurs in cirrhosis and when the spleen is infiltrated with leukemic cells. The erythrocytes are vulnerable to stasis and are therefore lysed in the splenic cords. The resulting anemia stimulates the compensatory erythroid hyperplasia in the bone marrow.

II.C. ANEMIA OF BLOOD LOSS

With acute blood loss, the alterations reflect principally the loss of blood volume rather than the loss of hemoglobin. Shock and death may follow. If the patient survive, the blood volume is rapidly restored by shift of water from the interstitial fluid compartment. The resulting hemodilution lowers the hematocrit. Reduction of the oxygenation of tissues triggers the production of erythropoietin, and the marrow responds by increasing erythropoiesis.

Soon after the acute blood loss the red blood cells appear normal in size and colour. However, as the marrow begins to regenerate, there is an increase in reticulocyte count, reaching 10 to 15% after 7 days. The reticulocytes are seen as polychromatophilic macrocytes in the peripheral blood.

3. ERYTHROCYTOSIS (POLYCYTEMIA)

The term polycythemia signifies an increase above the normal in the number of red blood cells in the circulating blood. The increase may or may not be associated with an elevation in the total quantity of red blood cells in the body. It is important to distinguish between absolute polycythemia (an increase in the total red cell mass) and relative polycythemia, which occurs when, through loss of blood plasma, the concentration of the red cells becomes greater than normal in the circulating blood. This may be the consequence of abnormally lowered fluid intake, of the loss of

plasma in the interstitial fluid, or of the marked loss of body fluids, such as occurs in persistent vomiting, severe diarrhea, copious sweating, or acidosis.

Because the term polycythemia is used loosely to refer to all varieties of increase in the number of red corpuscles, the terms erythrocytosis and erythremia are preferred in referring to row forms of absolute polycythemia. Erythrocytosis denotes absolute polycythemia which occurs in response to some known stimulus (secondary polycythemia); erythremia (polycythemia vera) refers to the disease of unknown etiology.

Table 26 - Pathophysiologic classification of Polycythemia

Relative	Reduced plasma volume (hemoconcentration)
Absolute	
Primary:	Abnormal proliferation of myeloid stem cells, normal or low erythropoietin levels (polycythemia vera)
Secondary:	Increased erythropoietin levels Appropriate: lung disease, high-altitude living, cyanotic heart disease Inappropriate: erythropoietin secreting tumors (e.g. renal cell carcinoma, hepatoma, cerebellar hemangioblastoma)

Effect of polycythemia on the circulatory system

Because of the greatly increased viscosity of the blood in polycythemia, the flow of blood is often sluggish. Thus, the increased viscosity tends to decrease the rate of venous return to the heart. On the other hand, the blood volume is greatly increased in polycythemia, which tends to increase the venous return. Actually, the cardiac output in polycythemia is not far from normal because these two factors more or less neutralize each other.

The arterial pressure is normal in most people with polycythemia, although in about one third of them the pressure is elevated. This means that the blood-pressure regulating mechanisms can usually offset the tendency for increased blood viscosity to increase peripheral resistance and, thereby, to increase arterial pressure. Beyond certain limits this regulation fail.

In polycythemia vera the viscosity of blood sometimes increases from the normal of 3 times the viscosity of water to 10 times that of water. As a result the entirely vascular system becomes intensely engorged. In addition many capillaries become plugged by the viscous blood.

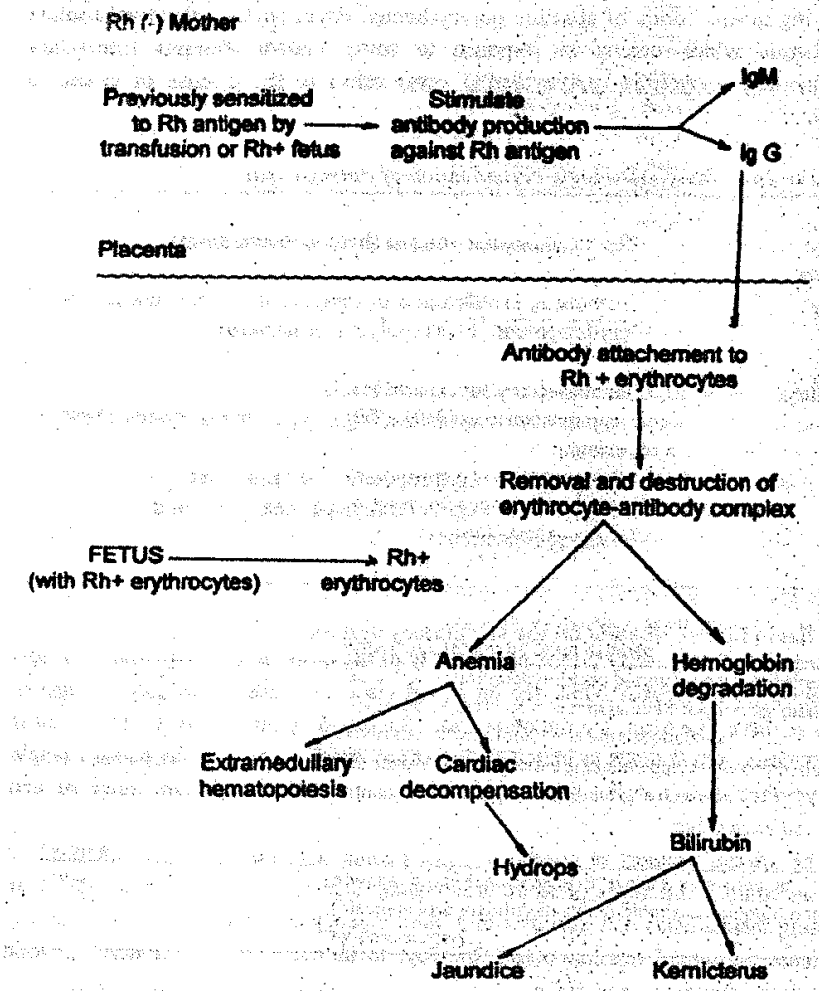


Figure no. 33. Pathogenesis of erythroblastosis fetalis

The color of the skin depends to a great extent on the quantity of blood in the subpapillary venous plexus. In polycythemia vera, the quantity of blood in this plexus is greatly increased. Furthermore, because the blood passes sluggishly through the

skin capillaries before entering the venous plexus, a larger than normal quantity of hemoglobin is deoxygenated before the blood enters the plexus. The blue color of this deoxygenate hemoglobin masks the red color of the oxygenated hemoglobin. Therefore, a person with polycythemia vera has ordinarily has a ruddy complexion with a bluish (cyanotic) tint to the skin.

Besides cyanosis, the clinical features of polycythemia include dizziness, headache, epistaxes, and increased incidence of thrombotic complications.

II.5.2. PATHOPHYSIOLOGY OF HEMOSTASIS

Hemorrhagic disorders

They are disorders characterised by a tendency to bleed.

Hemostasis means the arrest of hemorrhage at site of vascular injury. The interruption of bleeding from an injured blood vessel requires the combined activity of endothelial (vascular) cell, platelet and plasma factors, counterbalanced by mechanisms to limit the accumulation of platelets and fibrin to the area of injury.

Hemostatic abnormalities can lead to excessive bleeding or thrombosis.

NORMAL HEMOSTASIS

When a vessel is severed it almost immediately contracts (vasoconstriction), owing to reflex neurogenic mechanisms, possibly augmented by such humoral factors as endothelin, a potent endothelium-derived vasoconstrictor. Such vascular contraction is most evident in vessels that have well-defined muscular walls, but also occurs in the sphincteric mechanisms, situated at the junction of metaarterioles and capillaries, thereby shutting off capillary beds. Soon, however, the vascular spasm abates and bleeding would resume where it not for activation of the platelet and coagulation systems.

Hemostasis is achieved by the following processes (fig.no34):

A. endothelial cell injury-vascular damage

B. platelets adhesion and aggregation

C. the coagulation system

A. VASCULAR FACTORS

Vascular factors reduce blood flow from trauma by local vasoconstriction (an immediate reaction to injury) and by compression of injured vessels by blood extravasated into surrounding tissues.

The role of the endothelial cells

Blood is normally separated by the endothelial cells from the activators of hemostasis. Endothelial cells also modulate several aspects of the hemostasis-coagulation sequence. On the one hand they possess antithrombotic, antiplatelet, anticoagulant, and fibrinolytic properties; on the other hand they exert prothrombotic and procoagulant functions. The following are the properties of the endothelium that oppose clotting.

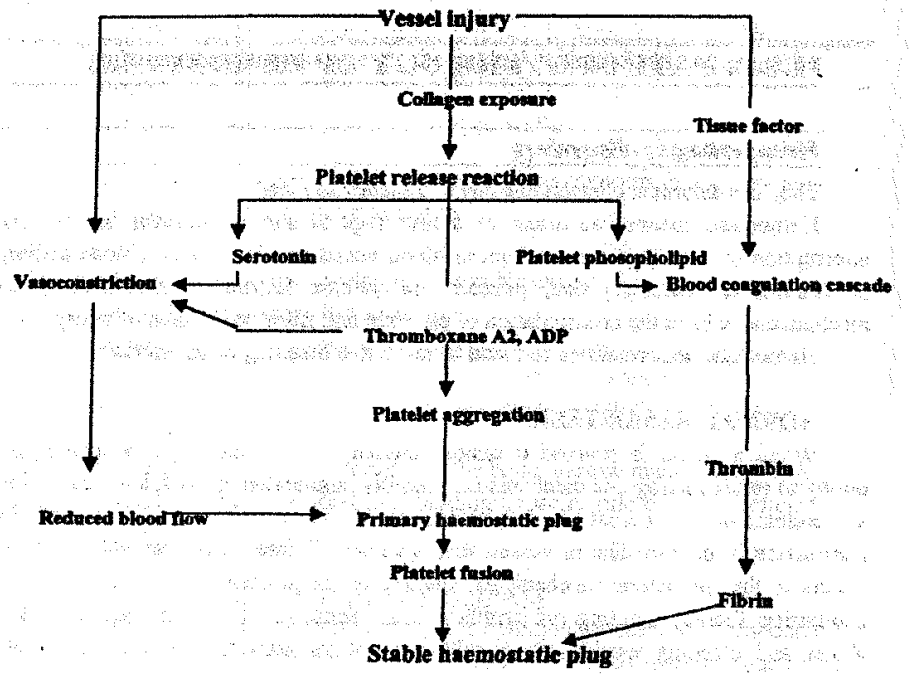


Figure no. 34
Reactions involved in hemostasis

Antiplatelet properties. Intact endothelium insulates the blood platelets and coagulation and proteins from the highly thrombogenic subendothelial components, principally collagen. Platelets flowig in the blood-stream do not adhere to the endothelium. This antiplatelet function seems intrinsic to the plasma membrane of endothelium and is not dependent upon the production of prostacyclin (PgI2). On the other hand, once platelets are "activated" (following focal endothelial injury), they are inhibited from adhering to the surrounding uninjured endothelial cells by the action of PgI2 and nitric oxide, which are powerful inhibitors of platelet aggregation and potent vasodilators. PgI2 is a well known arachidonic acid derivative whereas nitric oxide,

an endothelium-derived relaxing factor, is generated by enzymatic transformation of L-arginine. Their synthesis in endothelial cells is stimulated by adenosine dyphosphate (ADP), thrombin, cytokines and other undefined serum factors produced during coagulation.

Anticoagulant properties. Thesse are mediated by membrane-associated heparin-like molecules and thrombomodulin, a specific thrombin receptor. The heparin-like molecules act indirectly; they catalyze the actions of naturally occurring anticoagulant protein **antithrombin III**, which inactivates thrombin and several other coagulation factors including factor Xa. **Thrombomodulin** also acts indirectly. It binds thrombin and in so doing converts thrombin from a procoagulant to an anticoagulant.

Thrombin that is bound to thrombomodulin activates protein C, a powerful naturally occurring anticoagulant. Activated protein C inhibits clotting by proteolytic cleavage of factors Va and VIIIa. Protein S, synthesised by endothelial cells servs as a cofactor for the anticoagulant activity of protein C.

Fibrinolytic properties. Endothelial cells react against blood clotts by synthesising plasminogen activators that promote fibrinolytic activity in the blood and help to clear fibrin deposits from endothelial surfaces.

While on the one hand endothelial cells oppose blood clotting and thrombosis, on the other hand they are prohemostatic, affecting both platelets and coagulation proteins. As mentioned earlier, endothelial injury leads to the first step in hemostasis: adhesion of platelets to subendothelial collagen. Endothelial cells synthesize and secrete Von Willebrand's factor (vWF), which is essential for the adhesion of platelets to collagen and other surfaces. Tissue factor released from endothelial cells that have been injured or perturbed (e. g. by exposure to tumor necrosis factor (TNF) of interleukin 1 (IL1)) activates the extrinsec clotting pathway. Endothelial cells are also known to express binding sites for activated forms of factors IX and X, and cell-bound factors seem to be more active than their counterparts in solution. Another prothrombotic effect of endothelial cells is mediated through the secretion of an inhibitor of plasminogen activator, which depresses fibrinolysis.

Table 27 - . The prothrombotic and antithrombotic properties of the endothelium

Antithrombotic properties	Prothrombotic properties
Inhibition of platelet aggregation PgI2 NO ADP-ase	Stimulation of platelet agggregation and adhesion Von-Willebrand factor Platelet-activating factor
Anticoagulant-binding and induction of thrombin Antithrombin III acceleration by heparin molecules Thrombomodulin activation of protein C/S Alpha2-macroglobulin	Procoagulant factors Tissue factor Binding factors IXa,IX Factor V
Fibrinolysis Tissue plasminogen activator	Inhibition of fibrinolysis TPA inhibitor

Intact endothelial cells, although multifunctional, predominantly serve to inhibit platelet adherence and initiation of blood clotting. Conversely, injury to endothelial cells represents a loss of anticlotting mechanisms and thus contributes to hemostasis and to thrombosis.

B. PLATELETS

Platelets play a key role in normal hemostasis. Despite their lack of nucleus and tiny structure, thrombocytes are amazingly versatile. In their circulating form, they appear as relatively smooth discs enclosed within a typical plasma membrane; itself coated by a glycocalyx. Within the platelets there are two specific types of granules. Alpha-granules contain fibrinogen, fibronectin, factors V and VIII, vWf, platelet factor 4 (a heparin-neutralizing polypeptide) and platelet derived growth factor (PDGF). The other form of granules are electron-dense bodies that are the storage sites for a non-metabolic pool of adenine nucleotides (ADP, ATP) ionized calcium, histamine, 5HT and epinephrine.

With injury to a vessel, platelets are exposed to a number of elements in the vascular wall - subendothelial collagen, capillary basal lamina, fibroblasts, smooth muscle cells. Although all are capable of causing platelet adhesion, collagen is the most powerful stimulus. On contact with collagen, platelets undergo a number of changes, which can be listed as adhesion, release reaction (secretion) and aggregation. Together, these phenomena are referred to as platelet activation.

Platelet adhesion to collagen is the first step in the formation of hemostatic plugs. Circulating platelets do not adhere to normal endothelium or to each other until a vessel's endothelial lining is broken to expose subendothelium. Adhesion requires participation of an endothelial-cell secretion of the protein called vWf (found in the vessel wall and in plasma); vWf binds during platelet adhesion to a glycoprotein (GP) receptor of the platelet surface membrane (GP 1b) (figure no. 35).

Next, collagen and the first thrombin formed at the injury site activate platelets. These reactions activate phospholipase C, an enzyme that hydrolyses specific membrane phospholipids called inositol phospholipids. Products of this reaction activate protein kinase C and also increase the calcium concentration of platelet cytosol. As a result, series of progressive, overlapping events ensue:

Platelets change shape and develop long pseudopods

A receptor is assembled on the platelet surface membrane from GP II2 and GP IIIa.Fibrinogen and other adhesive proteins bind to this receptor causing platelets to stick to each other (platelet aggregation).

Arachidonic acid liberated from membrane phospholipids is oxidized to products that include:

a. prostaglandin H2, an important cofactor for the collagen-induced platelet activation.

b. thromboxane A2 that can also activate platelets.

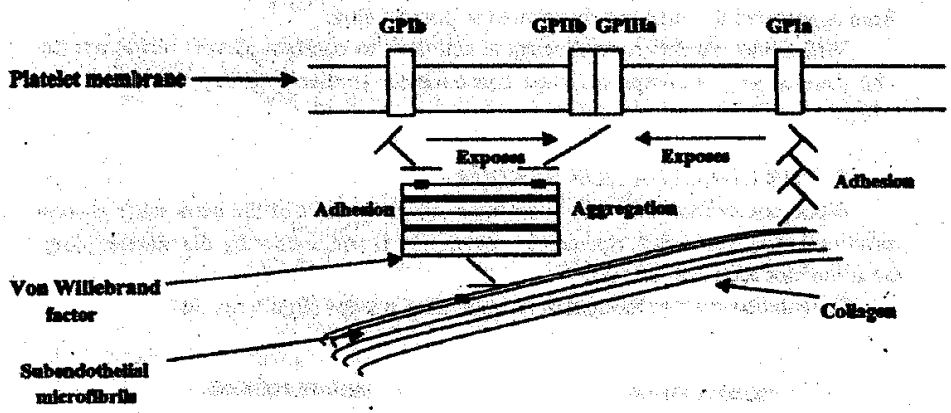


Figure no. 35

Platelet adhesion. The binding of glycoprotein (GP) Ib to von Willebrand factor leads to adhesion to the subendothelium and also exposes the GP IIB/IIIa binding sites to fibrinogen and von Willebrand factor leading to platelet aggregation. The GP Ia site permits direct adhesion to collagen

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b. thromboxane A2 that can also activate platelets.

Platelet contents are secreted; one material, ADP, can also activate platelets and recruit new platelets into the growing hemostatic plug.

On the platelet surface, the membrane reorganizes to expose phospholipids that are needed before enzyme / cofactor complexes of coagulation can form. Secretion of platelet factor 3 from the platelet alpha granules provides another key component for one of the enzyme / cofactor complexes. Thus, increasing amounts of thrombin are

generated that clot fibrinogen with formation of fibrin strends that radiate outward from aggregated platelets to help secure the platelet plug.

Within the platelets a mechanism is activated to contract platelet actinomyosin. The platelet plug is compressed and consolidated, further securing it to the site of injury.

C. THE COAGULATION SYSTEM

Blood coagulation reactions form the third component of the hemostatic process resulting in the **fibrin clot**. Spreading outward from and anchoring the platelet plugs, the fibrin clot adds needed bulk.

Coagulation may be thought of as occurring in steps (figure no. 36)

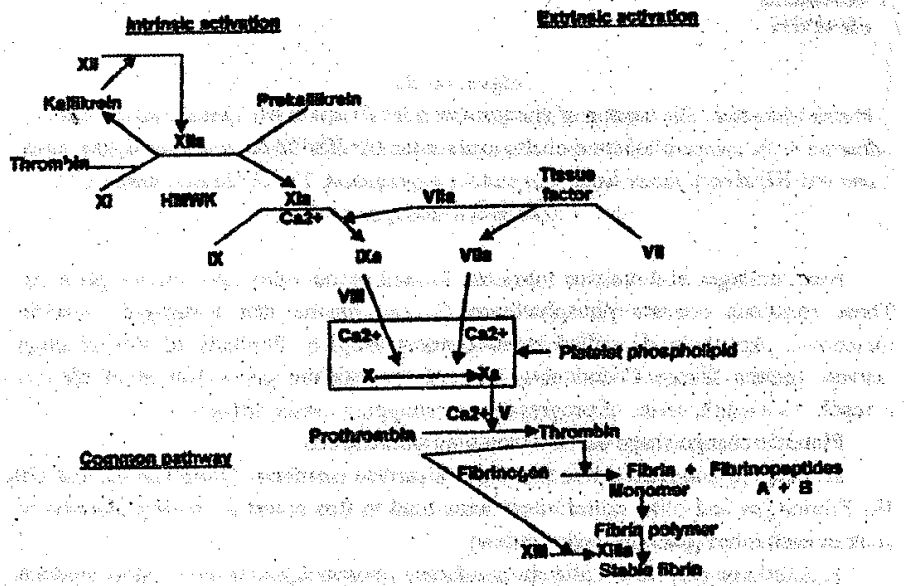


Figure no. 36

The pathways of blood coagulation. The intrinsic pathway in vivo begins with the activation of factor IX by factor VIIa. The factor XII and kallikrein reactions are probably relevant in in vitro tests only. Factor XI in vivo is activated by thrombin.

Ca, calcium; HMWK, high-molecular weight kininogen

Sequences of reactions in at least two pathways activate serine protease proenzyme with resultant formation of a prothrombin activator, which is a complex

(of an enzyme, factor Xa and two cofactors - factor Va and procoagulant phospholipid) present on the surface of activated platelets or of tissue cells.

The prothrombin activator cleaves prothrombin into two fragments, one of which is the enzyme thrombin.

Thrombin, by cleaving small peptides from the alpha (fibrinopeptide alpha) and beta (fibrinopeptide beta) chains of fibrinogen, gives rise to an altered molecule (fibrin monomer) that then polymerises to form insoluble fibrin (fibrin polymer).

Thrombin also activates factor XIII, an enzyme that catalyzes formation of collagen bounds between fibrin molecules, cross-linking the molecules to form a clot resistant to dissolution (figure no. 36).

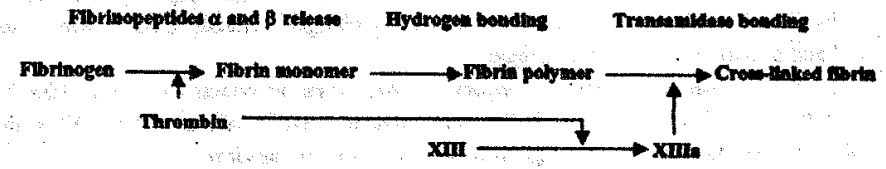


Figure no. 36

The formation and stabilization of fibrin

The components of blood coagulation reactions are the following:

a. Plasma factors

I. Fibrinogen is the precursor of fibrin.

II. Prothrombin is a precursor of serine protease thrombin, which converts fibrinogen to fibrin, activates factors V, VIII and XIII and, when bound to thrombomodulin, activates protein C. It is a vitamin K-dependent factor.

V. Proaccelerin. When activated to factor Va, serves as a cofactor for the enyzme factor Xa in a factor Xa / Va / phospholipid complex that activates prothrombin. It is also present in platelet alpha granules and is inactivated by activated protein C.

VII. Proconvertin. It binds to tissue factor and is then activated to form enzymatic component of a factor VIIa / tissue factor complex that activates factors IX and X. It is a vitamin K dependent factor.

VIII. Antihemophilic globulin (AHC). When activated to factor VIIIa, serves as a cofactor for the enzyme factor Ixa in factor IXa / VIIIa / phospholipid complex that activates factor X. It is inactivated by activated protein. It has common properties with factor V. It circulates in plasma bound to vWf.

IX. Christmas factor. When activated to factor IXa, functions as the enzyme of a factor IXa / VIIIa / phospholipid complex that activates factor X. It is vitamin K dependent.

X. Stuart-Prower factor. When activated to factor Xa functions as the enzyme of a factor Xa / Va / phopholipid complex that activates prothrombin. It is vitamin K dependent.

XI. Plasma thromboplastin antecedent (PTA). When activated to factor XIa, activates factor IX in a reaction requiring no cofactor except calcium ions. It circulates as a biomolecular complex with HMWK.

Prekallikrein, Fletcher's factor participates in a reciprocal reaction of contact activation in which it is activated to kallikrein by factor XIIa and the kallikrein then catalyzes further activation of factor XII to factor XIIa. It circulates as a biomolecular complex with HMWK.

HMWK circulates as a biomolecular complex with either factor XI or prekallikrein. When absorbed onto a negatively charged surface, brings down factor XI and prekallikrein onto the surface.

XII, Hageman's factor, contact factor, when activated to factor XIIa by negatively charged surfaces or kallikrein, activates prekallikrein and factor XI in the contact activation reactions, triggering blood coagulation in vitro.

XIII, fibrin stabilizing factor, when activated by thrombin,catalyzes formation of peptide bonds between fibrin molecules, thus helping to stabilize the clot.

Protein C. When activated by thrombin bound to thrombomodulin, inhibits by proteolysis the cofactor activity of factors VIIIa and Va in a reaction requiring protein S and phopholipid as cofactors. It is vitamin K dependent.

Protein S. It exists in plasma as free protein S and as protein S bound to the C4b binding protein of the complement system. The free form functions as a cofactor for activated protein C. It is vitamin K dependent.

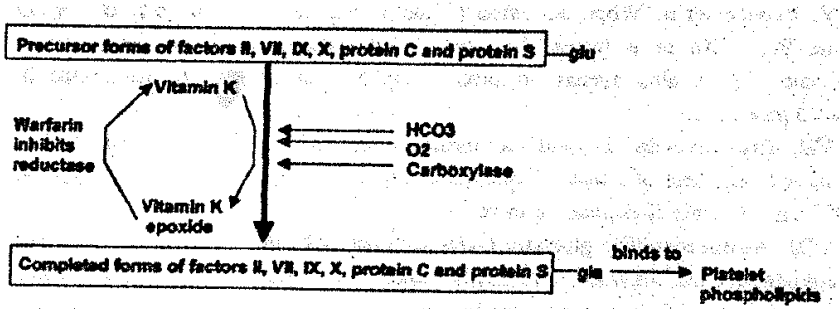


Figure no. 37

The role of vitamin K. Glu, glutamic acid; gla, gamma carboxylated glutamic acid

b. Surface factors

Tissue factor, tissue thromboplastin. It is a lipoprotein consitutively present on the membrane of certain tissue cells, including perivascular fibroblasts, epithelial cells at body / environment boundaries (e. g. epithelial cells on the skin, amnion and the gastrointestinal and genitourinary tracts), glial cells of the nervous system. Tissue factor may also develop in pathologic states on activated monocytes and macrophages and possibly on activated vascular endothelium and is present on some tumour cells. Binding of factor VII to tissue factor is the key reaction initiating blood coagulation in hemostasis.

Procoagulant phospholipid. It is an acidic phospholipid(primarily phosphatidyl serine) present on the present surface of activated platelets and other tissue cells.Functions as a component of the factor IX / VIIIa / phospholipid activator of factor X and of the factor Xa / Va phospholipid activator of prothrombin. It also functions as a lipid moiety of tissue factor.

Thrombomodulin, an endothelial cell surface binding site for thrombin. When bound to thrombomodulin, thrombin readily activates protein C.

Calcium (Ca) ions are needed in most thrombin generating reactions; thus, Ca-chelating agents (e.g. citrate or edetic acid) are used in vitro as anticoagulants. A number of serine protease proenzymes contain residues of an unusual aminoacid called gamma-carboxyglutamic acid that contains not one but two carboxy groups attached to the gamma-carbon of glutamic acid. The extra carboxy group creates binding sites for calcium. **Vitamin K** is needed for the reactions that attach the added carboxy group to glutamic acid; thus, the proteins containins gamma carboxy-glutamic acid residues are **called vitamin K-dependent clotting factors.** When synthetisised without vitamin K, these proteins cannot bind Ca normally nor function normally in blood coagulation.

It is customary to divide the blood coagulation scheme into an **extrinsec** and an **intrinsic** pathway, both of which converge at the point where the factor X is activated. There are several interconnections between the so-called intrinsic and extrinsic pathways. An important example of such "cross-talk" between pathways is the demonstration that the conversion of factor IX to factor IXa is brought out not only by the "contact-activated" factors of the intrinsic factors but also by factor VII, the initiator of the extrinsec pathway.

Reactions that generate the prothrombin activator complex may be initiated in vitro:

- by exposing plasma to a negatively charged surface (e. g. glass or certain diatomaceous earth powders) or
- by adding to plasma a tissue lipoprotein called tissue factor.

In the former, factor XII, high molecular weight kininogen (HMWK), prekalikrein and factor XI come down onto a negatively charged surface where they react (contact activation reactions) to give rise to activated factor XI. Factor XIa then activates factor IX. A factor X activator then forms as a complex of the enzyme, factor IXa and two cofactors, factor VIIIa and procoagulant phospholipid, the latter present on the surface of activated platelets or of tissue cells.

If a hereditary deficiency of factor XII, HMWK or prekallikrein occurs, the patient does not display bleeding abnormalities, whereas subjects with inherited factor XI deficiency display a mild bleeding disorder. Thus, an unidentified mechanism to activate factor XI that by-passes factor XII, prekallikrein, and HMWK must exist in vivo. Patients lacking factor IX (hemophilia B) or factor VIII (hemophilia A) bleed severely. This means that formation of the factor IXa / VIIIa phospholipid factor X activator is therefore essential for normal hemostasis.

When a tissue factor preparation and calcium ions are added to plasma in vitro, plasma factor VII very rapidly binds to the tissue factor .Surgical trauma that injures or severes small blood vessels causes blood to contact the tissue factor on membranes of cells within and beyond vessel walls. Factor VII / tissue factor complexes rapidly form with two consequences:

binding to tissue factor makes it possible for a trace concentration of factor Xa, preferencially and rapidly to convert the bound zymogen or VII to factor VIIa.

the tissue factor serves as a cofactor for fator VIIa that enables a factor VIIa / tissue factor complex to activate efficiently its two physiologic subtrates: factors IX and X (it is still unclear how the first molecules of factor Xa initiate the activation of factor VII bound to tissue factor at a wound site. Does plasma normally contain a minute concentration of circulating factor VIIa, which, on binding to tissue factor, catalyzes generation of the initial molecules of factor Xa?

Since the role of factor IXa is to activate factor X, the exposure of plasma to tissue factor effects activation of factor X **directly** by factor VIIa / tissue factor complexes and **indirectly** by factor IXa / factor VIIa / phospholipid complexes.

Two routes to factor X activation are required for normal hemostasis, presumably because the catalytic activity of factor VIIa / tissue factor is inhibited as coagulation proceeds by a Xa dependent mechanism. Thus, factor Xa plays a dual regulatory role in tissue-factor-dependent coagulation. The initial molecules start the reactions by switching factor VII bound to tissue factor to factor VIIa. However, as more factor Xa forms, factor Xa molecules begin to bind to plasma protease inhibitor, reffered to as either the extrinsec pathway inhibitor (EPI) or the lipoprotein associated coagulation inhibitor (LACI). The resultant EPI / Xa (LACI / Xa) complexes then bind to factor VIIa on tissue factor, giving rise to quaternary factor VIIa / tissue factor / EPI (LACI) / Xa complexes that lack catalytic activity. This inhibitory mechanism probably explains why hemophiliacs bleed; I.e, why the direct factor VIIa / tissue

factor activation of factor X, which bypasses the need for factor VIII and factor IX, does not suffice for normal hemostasis.

c. Regulatory mechanisms

Once the coagulation cascade has been activated, it must be contained to the local site of vascular injury lest clotting involve the entire vascular tree.

Regulatory mechanisms include:

- cellular clearance of activated clotting factors, especially during hepatic circulation
- neutralization within the blood of the enzymes and activated cofactors of coagulation.

In addition to EPI (LACI), other plasma protease inhibitors that can neutralize coagulation enzymes include antithrombin III, alpha 2 macroglobulin, alpha 1 antiprotease and heparin cofactor II.

The most important is **antithrombin III**, the primary inhibitor of the key enzymes thrombin, factor Xa and factor IXa. Adding heparin to blood in vitro converts antithrombin III from a slow to an instantaneous inhibitor of these enzymes (this is the mechanism for heparin's therapeutic effect). It is known that heparin-like chains (present on the luminal surface of vascular endothelium) enhance the function of antithrombin III in vivo. Heterozygotes for hereditary antithrombin III deficiency with 50% of normal antithrombin III levels have an increased risk for the thrombosis, which attests to the importance of this protease inhibitor in regulating coagulation. Homozygotes have not been identified.

Inhibtion of the cofactors, factors VIII and Va, involves two vitamin-K-dependent proteins: **protein C and protein S**. Thrombin, when bound to a receptor on endothelial cells called thrombomodulin, acquires the ability to cleave a small peptide from and so activate protein C. Activated protein C (APC) is a serine protease, which (with protein S and procoagulant phospholipid as its cofactors) catalyzed proteolysis of factors VIIIa and Va that destroys their cofactor function. Heterozygotes for hereditary protein C or protein S deficiency, who have levels of these factors in the 50% of normal range, are also at increased risk for thrombosis. Infants born with homozygous protein C deficiency may die in the new-born period with fatal thrombosis (neo-natal purpura fulminans).

The fibrinolytic system

It is activated by fibrin deposition.

The plasminogen-plasmin system (Figure no. 38)

It serves to break down fibrin and check fibrin polymerisation. The proteolytic conversion of plasminogen to its active form (plasmin) is accomplished either by

factor XII-dependent pathway-intrinsic activation-or plasminogen activators (PA)-extrinsic activation. There are three groups of PA-s.

The urokinase-like PA (uPA) is present in plasma and various tissues and activates plasminogen in the fluid phase.

Tissue-type PA (tPA) synthesised principally by endothelial cells is active when attached to fibrin. The affinity for fibrin makes tPA a much more useful therapeutic agent. The fibrin split products once released, serve as potent anticoagulants. Plasminogen is also activated by a bacterial product,

Streptokinase (exogenous or extrinsic activation).

By disolving fibrin, the fibrinolytic system helps keep open the lumen of an injured blood vessel. A balance between fibrin deposition and lysis mintains and remodes the hemostatic seal during the days required to repair an injury to vessel wall.

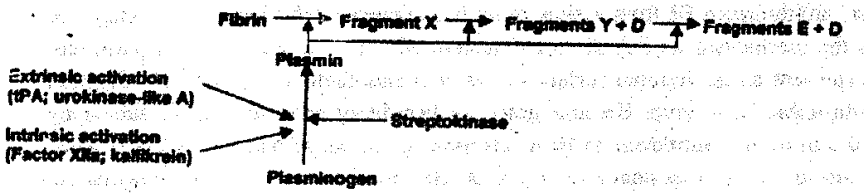


Figure no. 38
The fibrinolytic system

Bleeding disorders

Bleeding disorders are characterized by spontaneous bleeding or excessive bleeding following trauma, due to impairment of hemostasis. Such abnormal hemorrhage may result from:

- increased fragility of the vessels in vascular disorders
- inability to form an adequate platelet plug in platelet disorders
- defective endothelial-platelet interactions.

Vascular disorders

They may cause petechiae, purpura and bruising, but seldom lead to serious blood loss. Tests of hemostasis are usually normal. The diagnosis is made from other clinical findings.

Vascular purpuras may be grouped into:

I. hereditary disorders of angiogenesis or vascular structure and

II. acquired disorders incurred by vascular damage.

I. Hereditary vascular pupuras

They may result from inborn errors of collagen formation or of other elements of vascular support or from hereditary vascular malformations.

A. Purpuras subsequent to connective tissue disorders (genetic defects of collagen or elastic tissue metabolism) include Ehlers-Danlos' syndrome and Marfan's syndrome.

B. Purpuras consecutive to vascular malformations: Rendu-Osler-Weber's disease.

A. Ehlers-Danlos' syndrome and other hereditary connective tissue disorders

Bleeding may result from deficiencies of vascular and perivascular collagen in Ehlers-Danlos' syndrome and other rare hereditary connective tissue disorders, e. g. pseudoxantoma elasticum, osteogenesis imperfecta and Marfan's syndrome.

B. Hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber's disease)

It is an autosomal dominant vascular malformation affecting both men and women.

Diagnosis is made on physical examination by the discovery of characteristic small, red-to-violet telangiectatic lesions on the face, lips, oral and nasal mucosa, and the tips of the fingers and toes. Similar lesions may be present through the mucosa of the gastrointestinal tract and result in the major episodes of the gastrointestinal bleeding. Patients display repeated, profuse nosebleeds. Some patients may have associated pulmonary arteriovenous fistulas. **Laboratory studies** are usually normal, except for evidence of an iron deficiency anemia in most patients.

II. Acquired vascular purpuras

They include the following:

A. Mechanical purpuras

Purpura simplex (easy bruising)

It is the most common vascular bleeding disorder, manifested by increased bruising and representing increased vascular fragility. The patient, usually a woman during the reproductive period complains of bruises that develop without known trauma on the thighs, buttocks and upper arms. The history usually reveals no other abnormal bleeding, but there may be easy bruising in other family members. The platelet count and tests of platelet function, blood coagulation and fibrinolysis are all normal. No drug prevents the bruising; the patient is often advised to avoid aspirin but there is no evidence that the bruising is related to it.

Age-related vascular purpura (senile purpura)

It is a disorder affecting older patients, particularly those who have been exposed excessively to the sun, in whom deep purple ecchymosis, characteristically confined to the extensor surfaces of the hands and forearms, persist for a long time and may leave brownish discoloration due to the deposits of hemosiderin. New lesions appear without known trauma. The skin and subcutaneous tissue of the involved area often appear thinned and atrofic. No treatment helps.

B. Vasculitis

Allergic purpura (Henoch-Schonlein's or anaphylactoid purpura)

It is an acute or chronic vasculitis affecting primarily small vessels of the skin, joints, gastrointestinal tract and kidney. The disease affects primarily young children , but other children and adults with allergic purpura are also seen . An acute respiratory infection precedes the purpura in a high proportion of affected young children. Less commonly , a drug appears to the incinting agent , and a drug history should always be obtained.

Pathology and Pathogenesis

The serum often contains immune complexes with an Ig A component. Biopsy of acute skin lesion reveals an aseptic vasculitis with fibrinoid necrosis of vessel walls and perivascular cuffing of vessels with polymorphonuclear leukocytes. Granular deposits of reactive for Ig A and of complement components may be seen on immunofluorescent studies. Therefore, deposition of Ig A-containing immune complexes with consequent activation of complement is thought to represent the pathogenetic mechanism for the vasculitis. The typical renal lesion is a focal, segmental proliferative glomerulonephritis.

Symptoms, signs and clinical course

The disease begins abruptly, with the sudden appearance of a purpuric skin rash involving primarily the extensor surfaces of the feet and legs, a strip across the buttock and the extensor surfaces of the arms. Lesions may start as small areas of urticaria that progress to become indurated, palpable, purpuric spots. Crops of new lesions may appear over days to several weeks. Most patients also have fever and polyarthralgia with associated periarticular tenderness and swelling affecting the ankles, knees, hips, wrists and elbows. Many patients also develop edema of the hands and feet. Gastrointestinal findings are common and include colicki abdominal pain, abdominal tenderness and melena or stool tests positive for occult blood. From 25 to 50% of patients develop hematuria and proteinuria. The disease usually remits after about 4 weeks but often recurs one or more times after a disease-free interval of several weeks. In most patients the disorder then subsides without serious residual consequences; however, in some patients the renal lesion progresses to chronic renal failure.

C. Other acquired purpuric disorders include:

Septic purpura fulminans

Septicemia or viremia can cause vascular purpura by direct invasion of endothelium (as in rickettsial diseases), release of bacterial toxins damaging endothelium (as in meningococcemia), or igniting D.I.C. (as in gram-negative shock).

In fulminant meningococcemia, febrile and meningeal symptoms are often followed swiftly by peripheral vascular collapse, renal failure, necrotising cutaneous hemorrhages. Endotoxins released by Neisseria Meningitidis type C cause a virulent purpura with necrotising vasculitis.

Scurvy (vitamin C deficiency)

Hemorrhage may be a proeminent feature of scurvy. Perifollicular petechiae distributed over the thighs and buttocks is a characteristic finding. Large intramuscular hemorrhage and hemarthrosis also occur as well as periosteal hemorrhages in children.

Ascorbic acid (vitamin C) is an essential cofactor for hydroxylation of proline and lysine residues in collagen; these residues stabilize the hydrogen bonds responsible for its triple helical structure. In ascorbic acid deficiency unhydroxylated procollagen and collagen are unable to assume this stable conformation and newly formed collagen types III and IV so essential to vascular structure exist as randomly disoriented coils that are soon degradated. In scurvy, collagen wasting is most damaging to rapidly growing connective tissue structures such as hair follicles, gingival moorings and healing wounds.

Platelet disorders

Platelet disorders may cause defective formation of hemostatic plugs and bleeding because of decreased platelet number (thrombocytopenia-quantitative disorders) or because of decreased function despite adequate platelet numbers (platelet dysfunction-qualitative disorders).

Quantitative disorders

Quantitative disorders of platelets include (1) thrombocytopenia and (2) thrombocytemia.

1. Thrombocytopenia

Thrombocytopenia may stem from:

I. failure of platelet production

II. increased platelet destruction or utilisation or dilution of platelets

III. splenic sequestration of platelets

Table 28 - Classification of thrombocytopenic disorders

Etiopathogenesis of thrombocytopenia	Conditions
I. Failure of production	
1. Hereditary thrombocytopenias	Amegakaryocytic thrombocytopenia and the T.A.R. syndrome, Wiskott-Aldrich's syndrome
2. Diminished or absent megakaryocytes in marrow	Acquired megakaryocytic hypoplasia due to drugs and viral infections, leukaemia, aplastic anemia, paroxysmal nocturnal hemoglobinuria (some patients)
3. Abnormal production despite presence of marrow megakaryocytes (ineffective thrombopoiesis).	Alcohol-induced thrombocytopenia, thrombocytopenia in megaloblastic anemias, some myelodysplastic (preleukemic) syndromes.
II. Increased platelet destruction and/or utilisation	
1. Removal of antibody-coated platelets by mononuclear phagocytes	Acute and chronic idiopathic thrombocytopenic prupura (ITP), HIV-associated thrombocytopenia, posttransfusion purpura, drug-induced thrombocytopenia; thrombocytopenia concurrent to viral, bacterial and parasitic infections; neonatal thrombocytopenia; thrombocytopenia secondary to chronic leukaemia, lymphoma and SLE
2. Thrombin-induced platelet damage	States with intravascular coagulation: complications of obstretics, metastatic malignancy, gram-negative septicemia, traumatic brain damage.
3. Complex, multiple and poorly understood mechanisms	Thrombotic thrombocytopenic purpura, hemolytic-uremic syndromes, thrombocytopenia in adult respiratory distress syndrome, severe infections with septicemia.
III. Platelet sequestration in enlarged spleen leading to consumption by splenic macrophages	Cirrhosis with congestive splenomegaly, myelofibrosis with myeloid metaplasia, Gaucher's disease
IV. Dilution	Massive blood replacement or exchange transfusion (platelets lose viability in stored blood), cardiopulmonary by-pass surgery.

Regardless of cause, severe thrombocytopenia often results in a typical pattern of bleeding: multiple petechiae in the skin, often most evident on the lower legs; scattered small ecchymoses at sites of minor trauma; mucosal bleeding (epistaxis, gastrointestinal and gastrourinary tracts an vaginal bleeding); and excessive bleeding after surgery. Heavy gastrointestinal bleeding and bleeding into the CNS may be life-threatening manifestations of thrombocytopenic bleeding. However, thrombocyto-

penia does not cause massive bleeding into the tissues or hemarthrosis, such as may occur in bleeding secondary to plasma coagulation factor derficiencies (e. g. hemophilia).

A through drug history must be taken to rule out exposure to drugs known to cause increased platelet destruction in sensitive patients. About 5% of those receiving heparin may develop thrombocytopenia. Thus, it is important to establish whether a patient is receiving heparin. Since this is neither dose - nor route-dependent, it can occur even if the mere use of very low doses as with heparin flushes to keep intravenous or arterial lines open. Other drugs that less commonly induce thrombocytopenia in sensitive individuals include quinidine, sulfa preparations, oral antidiabetic agents, gold salts and Rifampin. Because patients infected with the human immunodeficiency virus (HIV) may present with an isolated severe thrombocytopenia otherwise indistinguishable clinically from idiopathic thrombocytopenic purpura (ITP), risk factors and history of other symptoms of HIV infection should be elicited. Other important points in a history may be a blood transfusion within 10 days (possible posttransfusion purpura), significant alcohol consumption (possible alcohol-induced thrombocytopenia) and symptoms (e. g. arthralgia, Raynaud's phenomena, unexplained fever) suggestive of an underlying immunologic disease.

Laboratory findings

The peripheral blood cell count establishes the presence and severity of thrombocytopenia and possible cause.

Platelet size-large platelets suggest compensatory increased platelet production, often found in thrombocytopenias secondary to increased platelet destruction or utilisation.

Bleeding time-prolonged accordingly to severity; in moderate thrombocytopenia (50,000 /microL), a very long bleeding time suggests that the cause (e. g. platelets coating with antibodies) has resulted in functional impairment of circulating platelets.

Other screening tests of hemostasis-normal

Bone marrow aspiration-number and appearance of megakaryocytes; confirmation of the impression gained from the peripheral blood smear of the presence or absence of disease causing marrow failure (e. g. leukemia).

Measurement of platelet associated Ig G may also be of value in selected patients.

If a patient receiving heparin becomes thrombocytopenic, a test for heparin-induced platelet aggregation of for heparin-dependent platelet release (of serotonin or ATP) should be carried out.

I. Diseases subsequent to failure of thrombocyte production

1. Amegakaryocytic thrombocytopenia and TAR syndrome

Hereditary amegakaryocytosis (thrombocytopenia with absent radii: TAR syndrome) is an autosomal recessive disorder in which thrombocytopenia caused by near-absence of megakaryocytes is associated with various somatic abnormalities, the most constant of which is bilateral radial aplasia. Mortality during the first year of life is about 40%, while survivors will further display hemorrhages interspaced with unexplained leukemoid bouts, that slowly abate as the platelet levels gradually rise and their malfunctions spontaneously correct.

2. Wiskott-Aldrich's Syndrome

This is a deadly X-linked disorder of males; a fruste forme, "amegakaryocytic thrombocytopenia is caused by a defect in the same gene on the short arm of chromosome X permitts subjects to survive adolescence. Wiskott-Aldrich's syndrome is characterised by thrombocytopenia, small platelets and failure of T-cell mediated immunity that leads to eczema, repetitive infections and a high risk of early death from fulminant sepsis or opportunistic lymphomas. Platelets are 50% of the normal volume and deficient in GPIb, the vWF receptor. Bleeding time is prolonged disproportionate to the thrombocytopenia.

3. Acquired Megakyryocytic Hypoplasia

Caused by drugs

Because of the short lifespan of platelets, drugs that block megakaryocyte formation by CFU-Megs can cause life-threatening thrombocytopenic purpura beginning as soon as two to three weeks. Myelosupressive agents such as methotrexate, cytosine arabinoside, cyclophosphamide, busulfan, nitrosureas, chlorothiazide, etc. inhibit megakaryocyte replication as a dose-dependent adverse effect. Megakaryocytopoesis may suffer a depression either rapid or intermediate in onset and subsidence, be gradually but persistently damaged or finally may be shut down completely and ineluctably.

Caused by viral infections

Viruses causing measles, varicella, cytomegalovirus syndrome, infectious mononucleosis, dengue and Thai hemorrhagic fever are megakaryocytotropic, adsorb to platelets and to megakaryocytes during viremia and undergo endocytosis. Platelet counts are reduced during infection and platelet aggregation and procoagulant activity are reduced resulting in severe bleding.

II. Diseases subsequent to increased platelet destruction, utilisation or dilution

1. Immunologic Idiopathic Thrombocytopenic Purpura (ITP)

It is usually a self-limited disorder subsequent to a viral infection in children, while most adults display a chronic disorder with no apparent predisposing cause.

In **acute (childhood) ITP**, viral antigen (Ag) is thought to trigger synthesis of antibody (Ab) that may react with viral Ag that has come down onto the platelet as viral Ag - Ab **immune complexes**.

Purpura follows abruptly one to two weeks after onset of a seasonal viral illness. Ig G antibodies attach to viral antigens adsorbed on platelet surfaces and when sufficient amounts of PA IgG accrue, platelet levels may plummet to counts below 20,000/microl, leading to petechiae, multiple ecchymosis and mucosal bleeding. Disease is self-terminated but during the first two weeks after onset in severe cases profuse bleeding and hemorrhagic bullae may appear.

In contrast, **chronic (adult) ITP** usually results from development of an auto-Ab (IgG antibodies) against a structural platelet Ag - the glycoproteins.

In both forms, either minimal or extensive petechiae, purpura and mucosal bleeding may be found on physical examination. Hemorrhagic bullae (blood blisters) may appear on the tongue or mucous membranes. Platelet count is diminished in peripheral blood while the percentage of the large forms is relatively increased. Bone marrow examination usually reveals increased number of megakaryocytes in an otherwise normal marrow.

2. Other Immunologic Thrombocytopenias

A patient infected with **HIV** may present with clinical findings differing from ITP only in having a positive test for HIV. Such patients may respond to adrenal glucocorticosteroids, danazol or both, but these drugs are often not given unless the platelet count falls below $\pm$ 30,000 / microL because of concern that they may further depress immune function. There are recent reports that the platelet count may rise after therapy with zidovudine (AZT).

Other disorders producing thrombocytopenia similar to ITP include immune thrombocytopenias secondary to a **collagen disorder** (e.g. **SLE**) or to **lymphoproliferative diseases**. Steroids and splenectomy are often effective in these forms of thrombocytopenia.

The clinical findings in **posttransfusion pupura** also closely resemble ITP except for a positive history of a blood transfusion within the preceding 7 to 10 days. The patient, usually a woman, lacks a platelet Ag (PLA-1) present in most people. The PLA-1 positive platelets in transfused blood stimulate formation of anti-PLA-1 which can also react with the patient's own PLA-1 negative platelets. Severe thrombocytopenia results taking two to six weeks to subside.

Some **drug-related immune thrombocytopenias** (e.g. **quinidine, quinine, gold salts, sulphonamide combinations and heparin induced thrombocytopenia**) also have findings identical to ITP, except for the history of drug ingestion. The drug promotes immunologic destruction of platelets and when the drug is stopped, the platelet count begins to increase within 7 to 10 days. An exception is **gold**-induced thrombocytopenia, since injected gold salts may persist in the body for many weeks.

In most instances, soluble drug or drug-protein complexes bind weakly to certain platelet glycoproteins. On rechallenge, Ig G antibodies are generated that bind via their Fab domains to platelets coated with drug, forming a stable antibody-drug complex on the platelet surface. The platelet receptors for drug-antibodies vary from drug to drug and among different patients exposed to the same drug, the principal receptors being components of GPIb, GPIIb, GPIIIa and GPIX. Depending on continued presence of the guilty drug, accumulation of sufficient numbers of antibody molecules on the platelet surface (Fc domain aimed outward) ensures lysis of the Ig-coated cells either by complement activation or by clearance from circulation by Fc gamma R-equipped macrophages.

Heparin-Induced Thrombocytopenia

It is the most important of the thrombocytopenias resulting from drug-related antibodies (Ab-s):

It occurs in up to about 5% of patients receiving bovine heparin and in 1% of those receiving procine heparin.

Rare patients within heparin-induced thrombocytopenia develop life-threatening arterial thrombosis (e.g. **thromboembolic occlusion** of limb arteries, **strokes**, acute myocardial infarction).

Thrombocytopenia results from the binding of heparin-Ab complexes to Fc receptors on the platelet surface membrane. Why a rare patient develops an associated arterial occlusion is unclear. The thrombus that causes the occlusion is "a wide thrombus" made up primarily of aggregated masses of platelets containing little fibrin.

When a patient receiving heparin becomes thrombocytopenic, a heparin-associated platelet aggregation test or a heparin-dependent platelet release test should be carried out. If either test is positive, therapy with an oral anticoagulant should be initiated and heparin should be stopped. In a patient with proximal leg vein thrombosis and a high risk for pulmonary embolism, additional measures (e.g. insertion of a Greenfield filter into the vena cava) may need to be considered to protect the patient for the several days needed for oral anticoagulants to become fully effective.

3. Disorders with Thrombocytopenia, Fragmented RBC-s and Hemolysis (multiple mechanisms)

They are disorders in which loose strands of fibrin are deposited in multiple small vessels; they include **Thrombotic Thrombocytopenic Purpura (TTP)** and the **hemolytic-uremic syndrome**. As blood flows past the fibrin strands, platelets and RBC-s are damaged and microangiopathic hemolytic anaemia and thrombocytopenia results. Platelet consumption within multiple small thrombi also contributes to the thrombocytopenia.

TTP is an acute, potentially fatal disorder characterized by:

Severe thrombocytopenia

Fragmented RBC-s on the blood smear (helmet cells, triangular-shaped RBC-s, distorted-appearing RBC-s)

Evidence of hemolysis (a falling Hb level, polycrhomasia on the blood smear, elevated reticulocyte count, elevated level of plasma LDH)

Fever

Changing manifestations of ischemic damage to multiple organs

These last include varying, bizarre CNS findings; fluctuating jaundice (with elevation of both direct and indirect bilirubin because of the combination of hemolysis and hepato-cellular damage); and proteinuria, hematuria and mild elevation of the BUN as evidence of renal damage. Patients may also experience episodes of abdominal pain and changing heart rhythms due to myocardial damage. These findings are associated with a characteristic pathologic lesion involving vessels in multiple organs-blend, platelet fibrin thrombi (without the infiltrations of granulocytes within and around vessels walls characteristic of vasculitis) localized primarily to arterio-capillary junctions.

III. Other Forms of Thrombocytopenia

Thrombocytopenia secondary to platelet sequestration in an enlarged spleen (**hypersplenism**) can occur in a variety of disorders that produce splenomegaly. It is an expected finding in patients with congestive splenomegaly due to advanced cirrhosis. In contrast to immune thrombocytopenias, the platelet count usually does not fall below about 50,000 / microL unless the disorder producing the splenomegaly also impairs the marrow production of platelets (as may occur in myelofibrosis with myeloid metaplasia). Splenectomy would correct the thrombocytopenia but is almost never indicated in the patient with moderate thrombocytopenia. Patients with **gram-negative sepsis** often develop thrombocytopenia. Its severity often parallels that of the infection. The thrombocytopenia has multiple causes: D.I.C., formation of immune complexes that can come down onto the platelets, activation of complement and deposition of platelets on damaged endothelial surfaces. Patients with **adult respiratory distress syndrome** also may become thrombocytopenic, possibly secondary to deposition of platelets in the pulmonary capillary bed.

2. Essential Thrombocytemia (ET)

ET is an uncommon myeloproliferative disorder distinguished by pronounced thrombocytosis, phlegmatic progression, and episodes of thrombotic or bleeding problems. Platelet count may be up to 1,000,000; 3,000,000 or even 10,000,000.

ET is a proliferative disorder of pluripotential stem cells; the somewhat limited clonal family includes red cells, platelets and granulocytes but not monocytes or lymphocytes. The overproduction of platelets reflects unbridled proliferation of precursive megakaryocytes in the absence of colony stimulating factors. Platelet

counts generally exceed 1,000,000 cells/microl and the disease may be first suspected by routine examination of the blood smear. Platelets may form swarms and drifts, and with disease progression giant platelets and megakaryocytes fragements enter the blood in increasing numbers. Marrow cellularity is normal or moderately increased.

Qualitative Disorders of Platelets

Patients with hemorrhagic problems in whom the bleeding time is prolonged and yet platelet counts are normal suffer from platelet malfunctions and impairment of primary hemostasis.

I. Hereditary Qualitative Disorders of Platelets

If symptoms commence early in life and laboratory findings follow the above mentioned pattern, an inherited qualitative disorder of platelets may be presumed.

1. Inborn Disorders of Platelet Adhesion

Bernard Soulier's (giant platelet) syndrome (BSS) is transmitted by two autosomal recessive genes and marked by very large platelets, mild thrombocytopenia and defective vWF-dependent platelet adhesion. Bleeding occurs because BSS platelets lack GPIb which bears the primary vWF receptor. BSS platelets aggregate normally in response to physiologic agonists but are not agglutinated by **ristocetin** in the presence of vWF - a presumptive indication that GPIb (the vWF receptor) is missing or deficient.

von Willebrand's Disease will be described further.

2. Inborn Disorders of Primary Aggregation

Glanzmann's Thrombasthenia is an autosomal recessive disorder marked by severe mucous membrane and postoperative bleeding, very long bleeding time, absent clot retraction and failure of platelets to aggregate in response to all physiologic agonists. It is a pure failure of primary platelet aggregation stemming from the lack (type I) or deficiency (type II) of the GPIIb-IIIa fibrinogen receptor. This prevents the receptor-mediated fibrinogen cross-linkages and precludes the platelet-platelet aggregation essential to formation of the platelet plug.

3. Inborn Disorders of Platelet Secretion

Dense-body deficiency and other storage pool diseases (SPDs) encompass alpha SPDs, delta SPDs and alpha-delta SPDs, according to the affected secretory granule.

Defects of thromboxane synthesis or responsiveness are caused by "aspirin-like" defects in the prostaglandin pathway of thromboxane synthesis.

II. Acquired Qualitative Disorders

Bleeding commonly complicates chronic systemic diseases. Pathogenesis involves immunologic and metabolic imbalances, chronic fibrin degradation and antiplatelet medications. Bleeding time is abnormal while platelet counts are normal; patients cannot form a sound platelet plug.

1. Uremia

Serious bleedings in mucocutaneous areas are prevalent during uremia. Platelet synthesize subnormal amounts of thromboxane A2, whereas blood vessels elaborate a surplus of the platelet inhibitor, prostacyclin (Pg I2); the true antiaggregatory maladjustements work in synergy to engender bleeding.

2. Myeloproliferative and Myelodysplastic Disorders

Loss of alpha-adrenergic receptors and hence of aggregation by epinephrine, impaired oxydation of arachidonic acid by the lipooxygenase pathway and an instability of dense granules leads to depression of granular ADP as the platelet circulate. Many of these platelets look peculliar, dysplastic; they may be very large, sometimes representing megakaryocytes fragments composed of multiple territories.

Bleeding dificulties in these patients subsequent to severe platelet functional abnormalities may precede evolution to AML by many months.

3. Drug Induced Platelet Dysfunction

Aspirin. Conventional doses of aspirin prolong the bleeding time within minutes of ingestion by inhibiting the second phase of platelet aggregation and secretion. Platelet secretory inhibition results from irreversible accetylation of a proportion of cyclooxygenase, blocking synthesis of thromboxane A2 and inhibiting aggregation for the remainder of the accetylated platelet's lifespan. Use of aspirin in analgesia should be avoided in all patients predisposed to bleeding and in those facing hemostatic challenges such as surgery of child birth.

Antimicrobial agents. Most of the beta-lactam antibiotics, particularly the penicillins, when infused in large doses or given to patients with impaired renal or hepatic function, attach to the platelet mambrane and block the binding of vWF and of platelet agonists such as ADP and epinephrine to their respective receptors. Platelet dysfunction is maximal 3 to 5 days after start of therapy and the antiplatlet effect may persist for up to two weeks after antibiotic infusions are discontinued.

COAGULATION DISORDERS

These disorders result from either **hereditary** or **acquired** deficiencies of the clotting factors.

A. Hereditary deficiencies of each of the coagulation factors characteristically occur singly. Hemophilia A (factor VIII deficiency) and hemophilia B (Christmas disease, factor IX deficiency), are transmitted as X-linked recessive disorders, whereas most others (like von Willebrand's disease) are autosomal disorders. These three conditions are the most frequently encountered.

B. Acquired coagulation disorders usually result from deficiencies of several clotting factors. Vitamin K deficiency can result in a severe coagulation defect since this substance is critical for the synthesis of clotting factors II, VII, IX, and X. The

liver is the site of synthesis of several coagulation factors; thus, parenchymal diseases of the liver are among the commonest causes of hemorrhagic diatheses. In addition, several liver diseases are associated with complex derangements of platelet function and fibrinogen metabolism, all of which contribute to the coagulopathy in liver disease. Two other less frequent conditions can involve disseminated intravascular coagulation (DIC) and development of circulating anticoagulants (which are usually antibodies to hemostatic factors).

A. Hereditary disorders

Hemophilias A and B and von Willebrand's disease are the most common of bleeding due to hereditary clotting factors deficiency and will be the topic of the further discussion.

Hemophilia A and von Willebrand's disease are caused by qualitative or quantitative defects involving factor VIII-von Willebrand's factor (vWF) complex.

Plasma factor VIII-vWF is a complex made up of two separate proteins that are coded by separate genes and are synthesized by different cells. Although vWF is produced by both endothelial cells and megakaryocytes, the former cells are the major source of plasma vWF. Liver is the major but not only site of synthesis of factor VIII. The two components of factor VIII-vWF complex, synthesized separately come together and circulate in the plasma as a unit that serves to promote clotting as well as platelet-vessel wall interactions necessary to ensure hemostasis. Factor VIII procoagulant protein or factor VIII is the first component, required for the activation of factor X in the intrinsic coagulation pathway, and its deficiency gives rise to hemophilia. Through noncovalent bonds factor VIII is linked to a much larger protein, von Willebrand's factor. The latter, which forms approximately 99% of the factor VIII-vWF complex, exists in the form of a series of multimers from 400.000 to 20.000.000 daltons. vWF can bind to both collagen and platelet membrane glycoprotein Ib, so that these structures adhere to one another. In vivo, vWF is crucial to the normal hemostasis, since it facilitates the adhesion of platelets to subendothelial collagen, and its absence in von Willebrand's disease leads to a bleeding diathesis. In addition to its function in platelet adhesion, vWF also serves as a carrier for factor VIII.

I. Hemophilias

Hemophilia A (factor VIII deficiency), which affects about 80% of the hemophiliacs, and hemophilia B (factor IX deficiency) have identical clinical manifestations, screening abnormalities and sex-linked genetic transmission. Specific factor assays are required to distinguish the two.

Genetic manifestations

Hemophilia may result from many different mutations of the genes for factors VIII (hemophilia A) and IX (hemophilia B): point mutations involving a single nucleotide, deletions of parts of the gene, and mutations affecting gene regulation. Because both factors VIII and factor IX genes are located on the X chromosome, hemophilia affects males almost exclusively. All daughters of hemophiliacs will be obligatory carriers, but all sons will be normal. Each son of a carrier will have a 50% chance of being either normal or hemophiliac and each daughter will have a 50% chance of being either normal or a carrier. By measuring factor VIII level and comparing it with the level of von Willebrand factor (vWF) antigen (Ag) it is possible to determine whether a female inheriting pedigree at risk for being a carrier is a true carrier of hemophilia A. Similarly, measuring the factor IX level will often identify the carrier of hemophilia B. Rarely, random inactivation of 1 of the 2 X chromosomes in early embryonic life will result in a carrier having low enough factor VIII or IX level to experience abnormal bleeding (hemophilia in women).

a. Hemophilia A (classic hemophilia)

Factor VIII (antihemophilic globulin) is an unstable glycoprotein currently belived to be synthesized in the liver. Factor VIII is a vital procoagulant component of the intrisic coagulation pathway. It usually circulates in plasma, forming a complex with another very large protein molecule, the von Willebrand factor. Factor VIII is found in freshly drawn human plasma, but has no activity in serum, and its activity is rapidly loss unless plasma is kept frozen.

Current terminology relating to factor VIII and its properties is as follows:

1. The procoagulant protein is designated factor VIII and circulates noncovalently bonded to vWF, forming a VIII/ vWF complex

2. When factor VIII participates in immune reactions, it is called factor VIII antigen (VIII:Ag)

3. When factor VIII coagulant activity or function is assessed, it is called factor VIII coagulant (VIII:C)

When factor VIII coagulant activity (VIII:C) is lost after normal plasma clots, factor VIII:Ag is still present.

The severity of the coagulation defect in hemophilic males (and the rare female issue of a hemophilic father and carrier mother) varies from family to family but runs true within families. Bleeding is proportional to the degree of reduction in residual factor VIII levels. The pathologic effects of hemophilia are directly due to recurrent hemorrhages, which can be either spontaneous or the result

of trauma. When factor VIII coagulant (VIII:C) levels are below 2 units/dl, spontaneous bleeding into tissues is severe and frequent. Plasma concentrations between 2 and 10 units/dl (normal range: 50 to 200) result in more moderate bouts of

spontaneous hemorrhage, and levels between 10 and 30 units/dl are associated with serious bleeding only in response to trauma, surgery, or vigorous dental procedures.

In severely affected patients, bleeding into joints and muscles, especially of the lower limb, can cause destructive changes. Initially intracapsular joint hemorrhages can result in pain and limitation of movement, followed by fibrous and eventually bony ankylosis of major joints. Intramuscular bleeding leads to fibrous contracture of muscles; this combined with joint changes leads to crippling deformities.

Dysfunctional factor VIII. If the majority (75%) of the hemophiliacs lack factor VIII activity subsequent to failure or deletion of gene expression, the remainder also have decreased or absent activity by producing an immunologically recognizable but functionless protein, the gene encoding a faulty, often truncated protein product that lacks cofactor activity.

b. Hemophilia B (Christmas disease)

About 15% as prevalent as "classic hemophilia", hemophilia B is clinically identical to hemophilia A; factor VIII is the cofactor for activating factor IX and neither works without the other. One form of the disease (factor IX, Seattle 2) has been shown to be the result of a single adenine nucleotide deletion.

The nature of the defect should be determined by factor IX assay. Factor IX is more stable than factor VIII, but is difficult to concentrate from donor blood. Plasma is a useful source of factor IX for the treatment of hemophilia B.

Symptoms and signs in both types of hemophilia

Different abnormal allelic hemophilic genes support different levels of factor VIII or IX activity. The patient with a factor VIII or IX level less than 1% of normal will have severe bleeding episodes throughout his lifetime. The first episode will usually occur before age 18. Minor trauma can result in extensive tissue hemorrhages and hemarthrosis which if not properly managed can result in crippling musculoskeletal deformities. Bleeding into the base of the tongue with airway compression may be life-threatening.

Patients with factor or IX levels in the 5% of normal range have mild hemophilia. They rarely have spontaneous hemorrhages; however, they will bleed seriously after surgery if not managed correctly.

Patients with a factor VIII or IX level in the 10 to 25% of normal range have even milder hemophilia but may also bleed excessively after surgery or dental extraction.

HIV infection in hemophiliacs

Most hemophiliacs treated with plasma concentrates in the early 1980s are infected with HIV. Their care should include instruction for preventing transmission of HIV.

II. Von Willebrand's syndrome

Von Willebrand's syndrome describes a related group of inherited disorders that are due to abnormalities of the factor VIII molecule and in which purpura is the common clinical manifestation. Von Willebrand's syndrome differs from hemophilia in two main ways:

1. It is inherited as an autosomal dominant or occasionally autosomal recessive characteristic.

2. Both factor VIII:Ag and factor VIII:C are ussualy reduced in this syndrome, although either can occasionally be normal.

The disease is caused by either quantitative or qualitative abnormalities in vWF mediated formation of platelet plugs, aggravated variably by reduced VIII:C activity affecting fibrin formation.

Based on the levels of factor VIII subunits, the mode of inheritance , and the results of platelet aggregation and other laboratory studies , eight subtypes of the syndrome have been recognized to date.

In all varieties there is abnormal endothelial and platelet function as well as factor VIII abnormalities.

Clinically, the syndrome is characterised by purpura , epistaxis, menorrhagia in women and rapid onset of abnormal bleeding after surgery or trauma. Patients who inherit the disease as an autosomal recessive trait are the most severely affected.

All types of the syndrome have prolonged bleeding time and PTT with a normal PT. The platelet count is normal but platelet aggregation in the presence of ristocetin is usually abnormal. The von Willebrand's factor, factors VIII:Ag and VIII:C are reduced in several types.

The disease,however , is often mild and many cases do not require treatment . In more severe forms, bleeding is controlled by giving either cryoprecipitate or the vassopressin analog, DDVAP.

Remarkable, when patients are given cryoprecipitate, or fresh plasma, their autologous production of factor VIII:C begins to rise over the following 24 hours. It is thought that the transfused vWF stimulates the synthesis of factor VIII:C and protects its elimination.

Table 29 - Main features of the hereditary disorders of blood coagulation factors

Deficiency	Screening test results	Comments
Factor XII HMWK PK	PTT long PT normal	Test tube abnormality without clinical bleeding. It must be distinguished by specific assays from factor deficiency in which postoperative bleeding may occur.
Factor XI	PTT long PT normal	AR. No excess bleeding after trauma. May have negative bleeding history after earlier surgery, yet still bleed excessively after next surgery. Diagnosis by specific assay.
Factor VIII Factor IX	PTT long PT normal	Factor VIII deficiency = hemophilia A; factor IX deficiency = hemophilia B. Sex-linked transmission. Severe bleeding.
Factor VII	PTT normal PT long	AR, rare. Severe deficiency (<2%) associated with serious bleeding including CNS bleeding. Levels >5% associated with mild or no bleeding.
Factor V,Xor prothrombin	PTT long PT long	AR,rare. Bleeding may be mild or severe. Heavy menstrual flow in women. Distinguish by specific assays.
Fibrinogen	In afibrinogenemia (fibrinogen < 10 mg/dl) no clotting in PTT, PT because machine endpoint not triggered. In hypofibrinogenemia (fibrinogen 70-100 mg/dl) PT often = 2 sec prolonged, PTT normal, thrombin time long	Severe bleeding in afibrinogenemia (homozygous state), minimal early bleeding after surgery in hypofibrinogenemia (heterozygous state).
Dysfibrinoge -nemia	Thrombin time long PTT often normal PT slightly prolonged	Manifestations vary: there may be excessive bleeding, teadency to thrombosis, wound dehiscence. Fibrinogen low by clotting assay but normal by immunologic assay.
Factor XIII	PTT normal PT normal Thrombin time normal Clot dissolves in 5M urea	AR, rare. There may be severe bleeding with hemarthrosis, delayed postsurgical bleeding, poor wound healing. Spontaneous abortions in women.
Protein C Protein S	PTT normal PT normal Thrombin time normal	Heterozygote state (=50%) associated with increased tendency to venous thrombosis. Homozygous protein C deficiency causes neonatal pupura fulminans. Diagnosis: usually by immunoassay of plasma antigen level. Activity assays are becoming available.

B. Acquired disorders

I. Vitamin K deficiency

Vitamin K encompasses two groups of fat-soluble naphtoquinone derivatives: vitamin K1 produced by plants, and vitamin K2 manufactured by microorganisms. It comes from dietary vegetables and intestinal flora and stored in hepatocytes; it is the precursor of prothrombin (factor II) and factors VII, IX and X and without vitamin K these factors are unable to bind calcium and exert their coagulant function. Deficiency of vitamin K can cause severe hemorrhage . The deficiency may be the

result of malabsorbtion , prolonged administration of oral antibiotics and prolonged parenteral nutrition.

The diagnostic feature of vitamin K deficiency is a prolonged PT corrected to normal by parenteral administration of vitamin K.

a. Dietary deficiency of vitamin K

The normal daily requirement for vitamin K1 is in the range of 0.1 to 0.5 microg/kg. Prothrombin levels may plummet in patients maintained on intravenous fluids and deprived of dietary sources, with bowel-sterilizing, broad spectrum antibiotics.Debilitated patients on fat-free diets.

b. Hemorrhagic disease of the newborn

In normal newborn infants vitamin K malnutrition occurs as a physiologic oversight. Infants with hemorrhagic disease of the new-born have very protracted Pts (the badge of vitamin K deficiency) and marked reductions of all vitamin K dependent proteins.

c. Vitamin K malabsorption

It is an uncommon complication of nontropical sprue or regional enteritis, particularly when deficient dietary intake, intestinal malabsorption, and oral antibiotics act in collusion.

Severe vitamin K deficiency also occurs subsequent to chronic biliary obstruction, the prolonged PT being shortened by vitamin K therapy.

d. Liver disease

Levels of all vitamin K-dependent clotting factors are depressed in any form of parenchymal liver disease as part of a general failure of protein synthesis that includes factor V but spares factor VIII. Concomitent deficiency of vitamin K dependent factors and of factor V is responsible for the long PT characteristic of liver disease.

Apart from failure to synthesize coagulant factors, liver disease incites baffling and shifting permutations of other hemostatic defects including thrombocytopenia, disseminated intravascular coagulation, increased fibrinolysis and dysfibrinogenemia.

e. Drug-induced vitamin K deficiency

Warfarin and other members of the coumarin family of anticoagulants inhibit synthesis of prothrombin and other vitamin K dependent factors by blocking vitamin K epoxide reductases. Patients present with "mysterious" bleeding and a vastly prolonged PT. During anticoagulant prophylaxis with warfarin, the interactions between the anticoagulant and other drugs that alter warfarin metabolism or action may precipitate bleeding crises.

II. Autoantibodies ("inhibitors") to hemostatic factors

They block clotting factors in subjects with no hereditary disorders. They are mostly circulanting IgG molecules. Factor VIII inhibition is a quite common clinical condition.

Autoantibodies to factor VIII may appear in a postpartum woman immediately or shortly after delivery, particularly if the patient suffers from an underlying autoimmune disorder, such as systemic lupus erythematosus, a lymphoproliferative

disorder, or sometimes in otherwise healthy elderly persons. IgG antibodies to factor VIII cause severe bleeding simulating hemophilia A. Screening tests reveal a protracted PTT and normal Pt and TT; normal plasma fails to correct the prolonged PTT. Generally, antibodies spontaneously disappear within 12 to 18 months of delivery and never return.

Thrombosis

A thrombus is formed within the circulation by an aggregation of various components of blood. Thrombi are soluble; bits broken off are known as emboli. Thromboembolic disease is much more common than abnormal bleeding and may affects arteries, veins or the heart.

Table 30 - Diseases associated with increased risk of thrombosis

Abnormality	Mechanism
Hereditary	
1. Antithrombin III deficiency	Impaired neutralization of serine proteases: thrombin, Xa, IXa
2. Protein C deficiency or protein S deficiency	Failure of proteolytic inhibition of the cofactors VIIIa and Va. Impaired activation of fibrinolysis
3. Homocystinuria	Damage to endothelium of arteries and veins by deposits of homocystine, causing "premature atherosclerosis"
4. Rare disorders of fibrinogeen and fibrinolysis	
a. Certain dysfibrinogenemias	Unknown, possibly impaired neutralization of thrombin by adsorption to fibrin, impaired binding to plasminogen
b. Abnormal plasminogen	Impaired formation of plasmin
Acquired	
1. Surgery, trauma, and the puerperium	Multiple thrombogenic risk factors
2. Carcinoma	Exposure of blood to tumor cells or tumor products with tissue factor activity
3. Hematologic proliferative disorders	
a. Acute promyelocytic leukemia	Release of tissue factor from primary granules
b. Myeloproliferative disorders (polycythemia, essential thrombocythemia)	Elevated blood viscosity, thrombocytosis, altered platelet membrane receptors and platelet responses
c. Paroxysmal nocturnal hemoglobinuria	Unknown, possibly defective (leaky) platelets
4. Lupus anticoagualant	Unknown, related to antibodies reacting with membrane phospholipids
5. Nephrosis	Multiple factors: markedly elevated fibrinogen, factor VIII; low antithrombin III from urinary loss; effects of hyperlipidemia on platelet function
6. Complications of therapy	
a. Oral contraceptives	Unknown, related to estrogen effects upon vessel wall and hemostatic factors
b. Infusion of prothrombin complex concentrates	Infusion of activated clotting intermediates
c. Heparin-induced thrombocytopenia	Unknown, related to intravascular aggregation of platelets

a. Arterial thrombosis

This usually occurs in atheromatous vessels but is also seen in normal arteries at sites of turbulent blood flow. Platelets adhere to diseased surfaces and the thrombus formed consists mainly of plataslets with a small amount of fibrin , a white thrombus.

Anticoagulants will not prevent the formation of thrombi composed mainly of platelets.Drugs inhibiting platelet function such aspirin may prevent further thrombosis.

Arterial emboli may derive from mural thrombi in the left ventricle , from the left atrium in mitral valve disease or from the surface of prosthetic heart valves. They also arise from aorta and large vessels , particulary the carotid arteries.

b. Venous thrombosis

This often occurs in normal veins. Important causes are stasis and hypercoagulability,. Stasis accompanies immobilisation from any cause and permits accumulation of activated coagulation factors and limits their dispersal, preventing contact with inhibitors. A red thrombus is formed, consisting mainly of red cells and fibrin. Emboli are thrown off from newly formed areas of thrombus.

Predisposing factors include local damage by cannulation and injections, varicose veins, surraunding inflammation , a previous history of thrombosis and advanced age. Increased blood viscosity is associated with both venous and arterial thrombosis and may be produced by changes in blood cells .as in polycythaemia, thrombocythaemia or sickle cell anaemia or by high levels of plasma protein as in mycloma or macroglobulinaemia.Depletion of inhibitors of coagulation has also been linked with venous thrombosis.The role of platelets ,the protein C system and prostacyclin release are at present uncertain.

Anticoagulant (heparin ,oral anticoagulants) and thrombolytic therapy aim to prevent further thrombosis and prevent embolisation while resolution takes place.

Disseminated intravascular coagulation (DIC)

Coagulation can be initiated by either the extrinsic pathway, which is triggered by the release of tissue factor ("tissue thromboplastin"), or the intrinsic pathway (through activation within the blood of factor XII by surface contact with collagen or other negatively charged substances). Both pathways lead to the generation of thrombin. The rapid clearance of activated clotting factors (factors Xa and XIa) by the reticuloendothelial system or by the liver; activation of endogenous anticoagulants (e.g., protein C); and activation of fibrinolysis inhibit clotting under normal conditions.

a. Definition

DIC is an acute, subacute or chronic thrombohemorrhagic condition that complicates a variety of diseases. It is characterized by widespread activation of the coagulation sequence with disseminated thromboses throughout the microcirculation,

resulting in consumption of platelets and coagulation factors and subsequent activation of fibrinolysis. Thus DIC may give rise either to tissue hypoxia and microinfarcts caused by myriad microthrombi or to a bleeding disorder related to pathologic activation of fibrinolysis and depletion of the elements required for hemostasis (hence the term consumption coagulopathy), or to both derangements.

b. Etiology and pathogenesis

Clinical disorders associated with DIC include: obstetric complications-abruptio placentae, retained dead fetus, septic abortion, amniotic fluid embolism; toxemia; infections-gram-negative sepsis, meningococcemia, malaria; neoplasms-pancreas, prostate, lung and stomach carcinomas; acute promyelocytic leukemia; massive tissue injury-trauma, burns, extensive surgery; miscellaneous causes-intravascular hemolysis, shock, vasculitis, hepatic failure.

The main causes of DIC are sepsis, obstetric complications, malignancy, and major trauma. The initiating factors in these conditions are multiple and often interrelated. For example, in obstetric conditions, tissue factor derived from the placenta, retained dead fetus, or amniotic fluid may enter the circulation; however, shock, hypoxia, and aciciosis often coexist and may cause widespread endothelial injury. Supervening infections may complicate the problem further.

DIC can be triggered through two pathways:

(1) Release of tissue factor or thromboplastic substances into the circulation from the placenta in obstetrical complications; from the cytoplasmic granules in the leukemic cells of acute promyelocytic leukemia; from mucin-secreting adenocarcinomas.

(2) Widespread injury to endothelial cells, following deposition of antigen-antibody complexes (in systemic lupus erythematosus), temperature extremes (in heat stroke or burns), infections with various microorganisms (e.g., meningococci and rickettsiae) and endotoxemia (such as in gram-negative sepsis, where there is also release of tissue factor, a strong thromboplastic substance with direct action). The final consequences are release of tissue factor, promotion of platelet aggregation and activation of the intrinsic coagulation cascade as a result of the exposure of subendothelial collagen Even subtle damage to the endothelium can unleash procoagulant activity by enhancing membrane expression of tissue factor.

DIC has two consequences. First, there is widespread fibrin deposition within the microcirculation, with subsequent ischemia of the more severely affected or more vulnerable organs and to hemolysis as the red blood cells are traumatized while passing through the fibrin strands (microangiopathic hemotytic anemia). Second, a bleeding diathesis follows as the platelets and clotting factors are consumed and there is secondary release of plasminogen activators. Plasmin can not only cleave fibrin-fibrinolysis-but also digest factors V and VIII, reducing their concentration further. Fibrinolysis leads to the formation of fibrin degradation products, which themselves

have an inhibitory effect on platelet aggregation, have antithrombin activity, and impair fibrin polymerization, all of which contribute to the hemostatic failure.

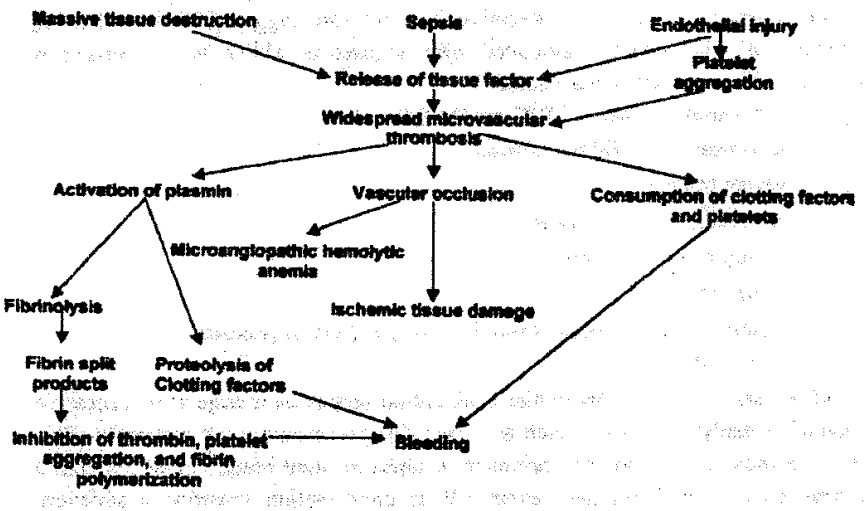


Figure no. 39
The pathophysiology of DIC

c. Clinical course

Association of a bleeding tendency in the face of evidence of widespread coagulation, with a wide variety of clinical manifestations. Abnormal clotting tipically occurs only in the microcirculation, although large vessels are involved occasionally. There may be shock with characteristic hypotension, renal failure, dyspnea, cyanosis, convulsions, coma. Clinical situations include postpartum bleeding; petechiae and ecchymoses on the skin; hemorrhage into the gut or urinary tract.

This is a complex syndrome caused by a widespread triggering of coagulation and fibrinolysis within the circulation. DIC occurs in a number of conditions when coagulation factors from both pathways are activated , leading to formation of thrombi throughout the microcirculation. As a consequence of the widespread thromboses there is consumption of platelets and coagulation factors and, secondarily, activation of fibrinolysis. If the vascular endothelium is extensively damaged, surface contact stimulates platelet and tissue factors which then activate both coagulation and

fibrinolysis. In DIC there is failure of inhibition of coagulation and secondar fibrinolysis follows.

Etiology. The triggering mechanism for DIC is the introduction into the circulation of various foreign substances , which may be the result of such diverse injuries as trauma, incompatible blood transfusion or snakebite. Severe infections especially those caused by gramnegative bacteria can trigger DIC by releasing endotoxin. DIC may also be associated with diseases in which tissue necroses is severe(transplant rejection,hepatic necrosis).

The most common causes of DIC are the following:

- incompatible blood transfusion
- severe trauma
- cardiopulmonary by-pass
- obstetric complications
- bacteriemia
- disseminated carcinoma from the prostate, lung or pancreas
- acute leukemia

Pathogenesis. When intravascular coagulation begins on a large scale excessive amounts of proteolytic enzymes such as factor Xa and thrombin are generated. This causes widespread conversion of fibrinogen to fibrin in small blood vessels. Within a short time circulating fibrinogen levels fall as consumption outstrips production. Concurently, there is intravascular aggregation of platelets, wich are removed from the circulation.

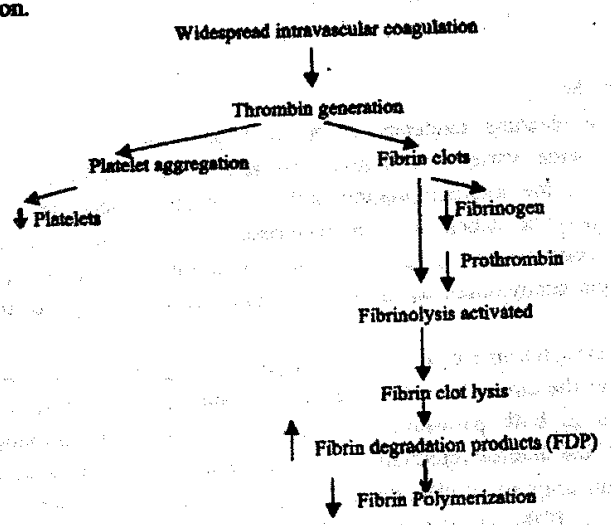


Figure no. 40

Pathogenesis of hemostasis abnormalities in DIC

The results of DIC are the following:

- fibrin deposition in capillaries
- plasma fibrinogen and factor IX, XI, prekallikrein and HMWK are reduced. This process is sometimes referred to as "consumption coagulopathy".
- the number of circulating platelets is reduced.

The hemorrhagic component of DIC results from:

- dissolution of clots causing bleeding from wound sites
- a fall in the levels of circulating fibrinogen
- an increase in the amount of breakdown products of fibrin and fibrinogen. These fibrin split products (FDP) are themselves anticoagulant and can increase the bleeding tendency.

Clinical features vary from no bleeding to complete hemostatic failure with widespread hemorrhage. This can occur from the mouth, nose or venal puncture sites and the skin shows widespread ecchymosis. The patient is often acutely ill and shocked, but the clinical severity varies according to the initiating factor.

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