Pathophysiology

Concepts of altered health status

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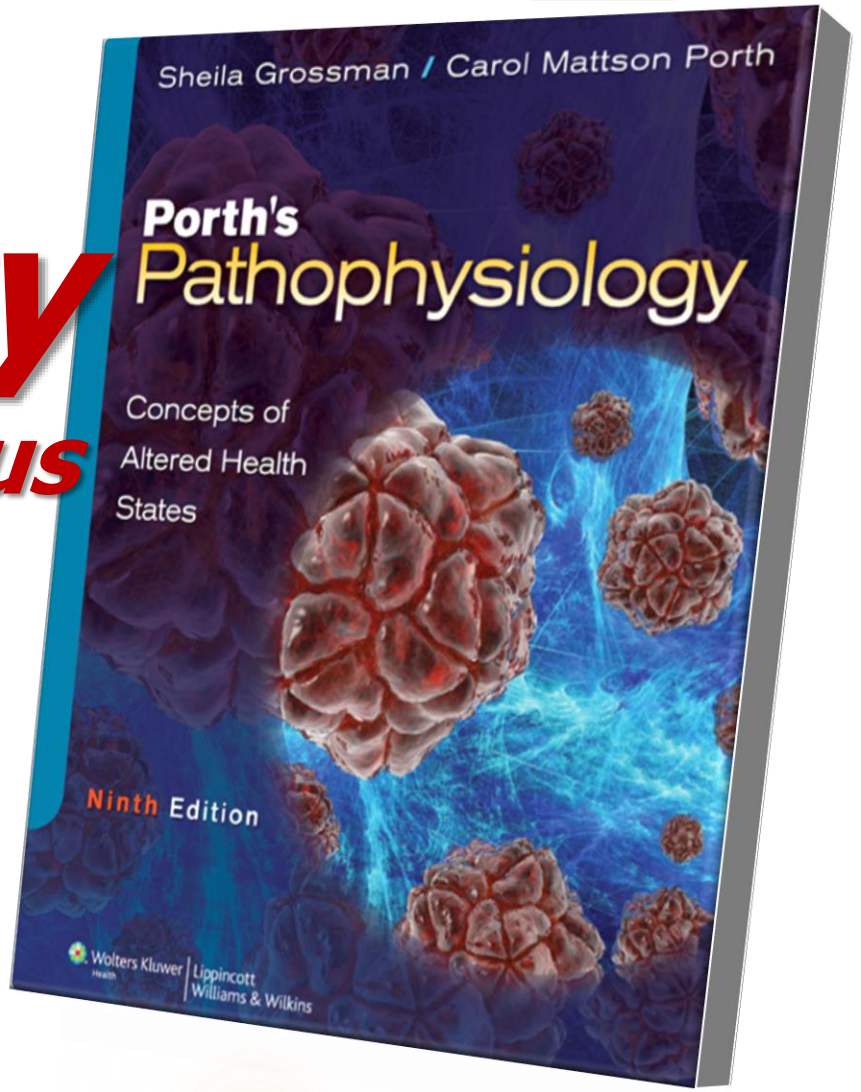


Definition and Meaning

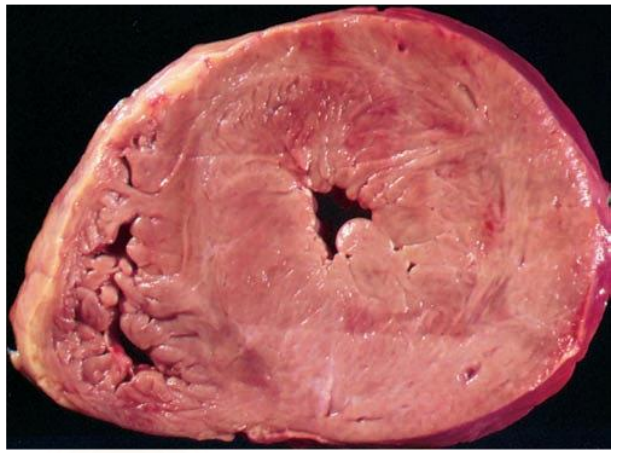
- The term *pathophysiology*, defined as the physiology of altered health.
- It combines the words *pathology* and *physiology*.
  - Pathology (from the Greek *pathos*, meaning “disease”) deals with the study of the structural and functional changes in cells, tissues, and organs of the body that cause or are caused by disease.
  - Physiology deals with the functions of the human body.

Definition and Meaning

- Pathophysiology also focuses on the mechanisms of the underlying disease

- provides information to assist with planning preventive as well as therapeutic health care measures and practices such as following a healthy diet, exercising, and being compliant with prescribed medications.

Atrophy of the frontal lobe of the brain.



Myocardial hypertrophy.

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Concepts of Health and disease

Health

Disease

Health

- According to the World Health Organization (WHO) in 1984, Health is defined as a "*state of complete physical, mental, and social well-being and not merely the absence of disease and infirmity,*"
- The U.S. Department of Health and Human Services in Healthy People 2020 describes the determinants of health as
  - 1. Attain lives free of preventable disease, disability, injury, and premature death
  - 2. Achieve health equity and eliminate disparities
  - 3. Promote good health for all
  - 4. Promote healthy behaviors across the life span

Disease

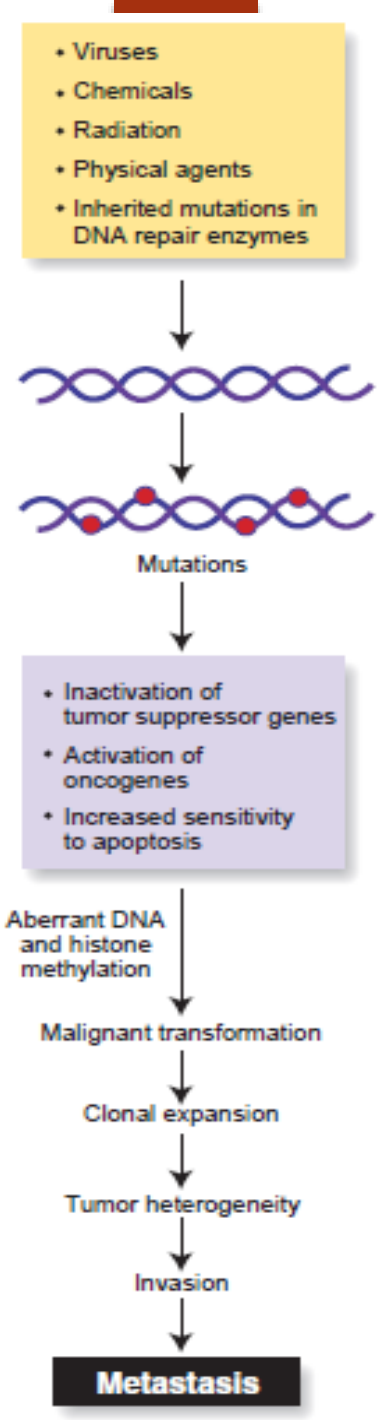
- A disease is considered an "*acute or chronic illness that one acquires or is born with that causes physiological dysfunction in one or more body system.*"
- Each disease generally has specific signs and symptoms that characterize its pathology and identifiable etiology.
- The aspects of the disease process include etiology, pathogenesis, morphologic changes, clinical manifestations, diagnosis, and clinical course.

- Etiology

- The causes of disease are known as *etiologic factors*
  - biologic agents (e.g., bacteria, viruses),
  - physical forces (e.g., trauma, burns, radiation),
  - chemical agents (e.g., poisons, alcohol),
  - genetic inheritance,
  - nutritional excesses or deficits.
- Most disease-causing agents are nonspecific, and many different agents can cause disease of a single organ.
- On the other hand, a single agent or traumatic event can lead to disease of a number of organs or systems (sickle cell anemia, familial hypercholesterolemia, . . .)

- Etiology

- the majority of diseases are multifactorial in origin. (cancer, heart disease, diabetes, . . .)
- The multiple factors that predispose to a particular disease often are referred to as *risk factors*.
  - *Congenital conditions* are defects that are present at birth, although they may not be evident until later in life or may never manifest.
    - genetic influences,
    - environmental factors (e.g., viral infections in the mother, maternal drug use, irradiation, or gestational position in utero),
    - a combination of genetic and environmental factors.
  - *Acquired defects* are those that are caused by events that occur after birth (injury, infectious agents, inadequate nutrition, lack of oxygen, inappropriate immune responses, and neoplasia).



- Pathogenesis

- *Pathogenesis* explains how the disease process evolves.
- pathogenesis is *the sequence of cellular and tissue events that take place from the time of initial contact with an etiologic agent until the ultimate expression of a disease*.
- Although etiology and pathogenesis are two terms often used interchangeably, their meanings are quite different.
  - For example, atherosclerosis often is cited as the etiology (or cause) of coronary artery disease. In reality, the progression of the inflammatory process from a fatty streak to the occlusive vessel lesion seen in people with coronary artery disease represents the pathogenesis of the disorder. The true etiology of atherosclerosis remains largely uncertain.

- Morphology and Histology

- *Morphology* refers to the fundamental structure or form of cells or tissues.
  - Morphologic changes are concerned with both the gross anatomic and microscopic changes that are characteristic of a disease.
- *Histology* deals with the study of the cells and extracellular matrix of body tissues.
  - Histologic sections play an important role in the diagnosis of many types of cancer.
- A *lesion* represents a pathologic or traumatic discontinuity of a body organ or tissue.
  - Descriptions of lesion size and characteristics often can be obtained through the use of radiographs, ultrasonography, and other imaging methods. Lesions also may be sampled by biopsy and the tissue samples subjected to histologic study.

- Clinical Manifestations

- Diseases can manifest in a number of ways.
  - Sometimes it is clear at the onset like manifestation of "fever"
  - Sometimes it is silent at the onset and is detected during examination for other purposes or after the disease is far advanced.
- A *symptom* is a subjective complaint that is noted by the person with a disorder, such as Pain, difficulty in breathing, and dizziness
- whereas a *sign* is a manifestation that is noted by an observer. An elevated temperature, a swollen extremity, and changes in pupil size are objective signs that can be observed by someone other than the person with the disease.

- Clinical Manifestations

- Signs and symptoms may be related to the primary disorder or they may represent the body's attempt to compensate for the altered function caused by the pathologic condition.
  - e.g. hemorrhage → tachycardia (increased HR)
  - e.g. decreased respiratory exchange → increased RR
- A *syndrome* is a compilation of signs and symptoms (e.g., chronic fatigue syndrome) that are characteristic of a specific disease state.
- *Complications* are possible adverse extensions of a disease or outcomes from treatment.
- *Sequelae* are lesions or impairments that follow or are caused by a disease.

- Diagnosis

- A *diagnosis* is the identifying the nature or cause of a health problem (e.g., bacterial pneumonia, . . .)
- The diagnostic process requires
  - a careful history, is used to obtain a person's account of his or her symptoms and their progression, and the factors that contribute to a diagnosis.
  - physical examination (PE), is done to observe for signs of altered body structure or function.
  - diagnostic tests are ordered to validate what is thought to be the problem. They are also performed to determine other possible health problems that were not obtained from the history and PE, but may be present given the signs and symptoms identified.

- Diagnosis

- a normal value for a laboratory test is established statistically from test results obtained from a selected sample of people. A normal value represents the test results that fall within the bell curve or the 95% distribution.
- The normal values for some laboratory tests are adjusted for gender, other comorbidities, or age.

- Laboratory parameters are interpreted based on the reliability, validity, sensitivity, and specificity of the measurement.

- Diagnosis

- *Validity* refers to the extent to which a measurement tool measures what it is intended to measure. For example, the validity of blood pressure measurements obtained by a sphygmomanometer might be compared with those obtained by intra-arterial findings, which are measurements obtained from invasive arterial catheters inserted into radial arteries of acutely ill people.
- *Reliability* refers to the extent to which an observation, if repeated, gives the same result. A poorly calibrated blood pressure machine may give inconsistent measurements of blood pressure, particularly of pressures in either the high or low range.

- Diagnosis

- *Sensitivity* refers to the proportion of people with a disease who are positive for that disease on a given test or observation (called a true-positive result).
  - If the result of a very sensitive test is negative, it tells us the person does not have the disease and the disease has been excluded or "ruled out."
- *Specificity* refers to the proportion of people without the disease who are negative on a given test or observation (called a true-negative result). Specificity can be calculated only from among people who do not have the disease.
  - A test that is 95% specific correctly identifies 95 of 100 normal people. The other 5% are false-positive results.

- Diagnosis

- Measures of sensitivity and specificity are concerned with determining how likely or how well the test or observation will identify people with the disease and people without the disease
- There are two possibilities for the test result to be correct (true positive and true negative) and two possibilities for the result to be incorrect (false positive and false negative).

		DISEASE	
		Present	Absent
TEST	Positive	True positive a	False positive b
	Negative	False negative c	True negative d

- Diagnosis

- *Predictive value* is the extent to which an observation or test result is able to predict the presence of a given disease or condition
- A positive predictive value refers to the proportion of true-positive results that occurs in a given population.
  - In a group of women found to have "suspect breast nodules" in a cancer screening program, the proportion later determined to have breast cancer would constitute the positive predictive value.
- A negative predictive value refers to the true-negative observations in a population.
  - In a screening test for breast cancer, the negative predictive value represents the proportion of women without suspect nodules who do not have breast cancer.

- Clinical Course

- The clinical course describes the evolution of a disease.
- A disease can have an acute, subacute, or chronic course.
- An *acute* disorder is one that is relatively severe, but self-limiting.
- *Chronic* disease implies a continuous, long-term process. A chronic disease can run a continuous course or can present with exacerbations (aggravation of symptoms and severity of the disease) and remissions (a period during which there is a decrease in severity and symptoms).
- *Subacute* disease is intermediate or between acute and chronic. It is not as severe as an acute disease and not as prolonged as a chronic disease.

- Clinical Course

- The spectrum of disease severity for infectious diseases, such as hepatitis B, can range from preclinical to persistent chronic infection.
- During the *preclinical stage*, the disease is not clinically evident but is destined to progress to clinical disease.
  - As with hepatitis B, it is possible to transmit a virus during the preclinical stage
- *Subclinical disease* is not clinically apparent and is not destined to become clinically apparent. It is diagnosed with antibody or culture tests.
  - Most cases of tuberculosis are not clinically apparent, and evidence of their presence is established by skin tests.
- *Clinical disease* is manifested by signs and symptoms.
- *Carrier status* refers to a person who harbors an organism but is not infected, as evidenced by antibody response or clinical manifestations. This person still can infect others.

Health and Disease in Populations

- Epidemiology and Patterns of Disease
  - Incidence and Prevalence
  - Morbidity and Mortality
- Determination of Risk Factors
  - Cross-Sectional and Case–Control Studies
  - Cohort Studies
- Natural History
- Preventing Disease
- Evidence-Based Practice and Practice Guidelines

Epidemiology and Patterns of Disease

- The health of people is closely linked to the health of the community and to the population it encompasses.
- The ability to traverse continents in a matter of hours has opened the world to issues of populations at a global level.
- Managed care systems are focused on a population-based approach to planning, delivering, providing, and evaluating health care.
- *Epidemiology* is the study of disease occurrence in human populations.
  - Epidemiology looks for patterns of people affected with a particular disorder, such as age, race, dietary habits, lifestyle, or geographic location.
  - Epidemiologist vs. biomedical researcher in smoking cigarette.

- Incidence and Prevalence

- Measures of disease frequency are an important aspect of epidemiology.
- They establish a means for predicting what diseases are present in a population and provide an indication of the rate at which they are increasing or decreasing.
- A *disease case* can be either an existing case or the number of new episodes of a particular illness that is diagnosed within a given period.
- *Incidence* reflects the number of new cases arising in a population at risk during a specified time.
  - The population at risk is considered to be people without the disease but who are at risk for developing it.
  - The cumulative incidence estimates the risk of developing the disease during that period of time.

- Incidence and Prevalence

- *Prevalence* is a measure of existing disease in a population at a given point in time (e.g., number of existing cases divided by the current population).
- The prevalence is not an estimate of risk of developing a disease because it is a function of both new cases and how long the cases remain in the population.
- Incidence and prevalence are always reported as rates (e.g., cases per 100 or cases per 100,000).

- Morbidity and Mortality

- *Morbidity* describes the effects an illness has on a person's life. Many diseases, such as arthritis, have low death rates but a significant impact on a person's life.
  - Morbidity is concerned not only with the occurrence or incidence of a disease but with persistence and the long-term consequences of the disease.
- *Mortality* statistics provide information about the causes of death in a given population.
  - Crude mortality rates (i.e., number of deaths in a given period) do not account for age, gender, race, socioeconomic status, and other factors. For this reason, mortality often is expressed as death rates for a specific population, such as the infant mortality rate.

Determination of Risk Factors

- Conditions suspected of contributing to the development of a disease are called *risk factors*. They may be inherent to the person (high blood pressure or overweight) or external (smoking or drinking alcohol).
- There are different types of studies used to determine risk factors, including *cross-sectional studies*, *case–control studies*, and *cohort studies*.

- Cross-Sectional studies

- *Cross-sectional studies* use the simultaneous collection of information necessary for classification of exposure and outcome status.
- They can be used to compare the prevalence of a disease in those with the factor (or exposure) with the prevalence of a disease in those who are unexposed to the factor,
  - for example, by comparing the prevalence of coronary heart disease in smokers and nonsmokers.

- Case–Control Studies

- *Case–control studies* are designed to compare people known to have the outcome of interest (cases) and those known not to have the outcome of interest (controls).
- Information on exposures or characteristics of interest is then collected from people in both groups.
  - For example, the characteristics of maternal alcohol consumption in infants born with fetal alcohol syndrome (cases) can be compared with those in infants born without the syndrome (controls).

- Cohort Studies

- A *cohort* is a group of people who were born at approximately the same time or share some characteristics of interest. People enrolled in a cohort study (also called a *longitudinal study*) are followed over a period of time to observe a specific health outcome.
- A cohort may consist of a single group of people chosen because they have or have not been exposed to suspected risk factors.
  - Framingham Study
    - Framingham, Massachusetts. From 1950 for 20 years. 5000 persons, between 30 and 59 years of age selected randomly. On developing coronary heart disease. 1500 of them developed the dz.
  - Nurses' Health Study
    - Harvard University. Began in 1976. include 238000 female nurses. 30 to 55 years of age. On the relationship between oral contraceptives and breast cancer. menstrual cycle, smoking habits, diet, weight and waist measurements, activity patterns, health problems, and medication use were studied.

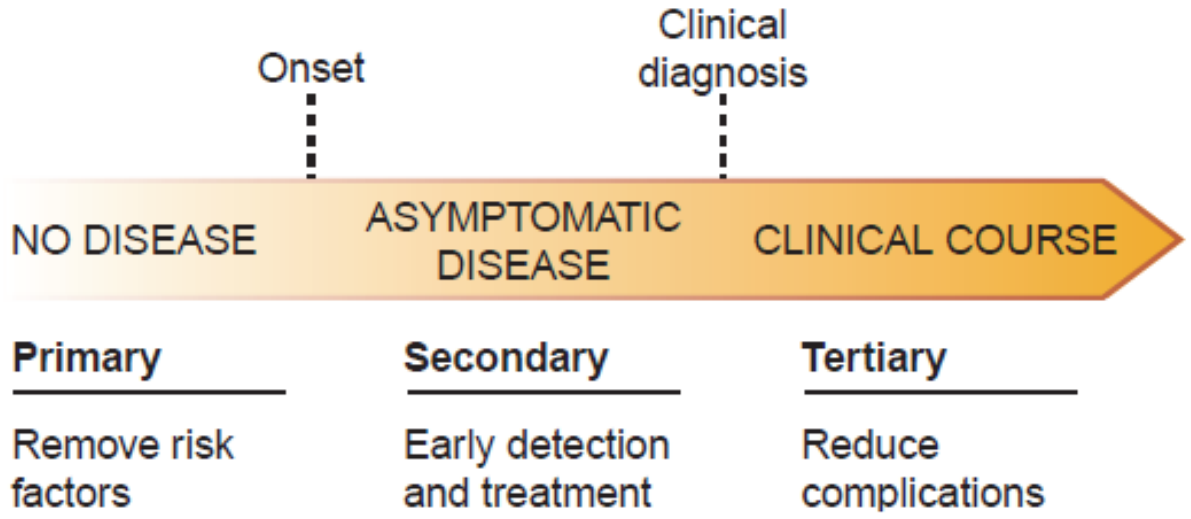
Natural History

- The *natural history* of a disease refers to the progression and projected outcome of the disease without medical intervention.
- By studying the patterns of a disease over time in populations, epidemiologists can better understand its natural history to determine:
  - disease outcome,
  - establish priorities for health care services,
  - determine the effects of screening and early detection programs on disease outcome,
  - compare the results of new treatments with the expected outcome without treatment.
  - the natural history of a disease which has no effective treatment methods available, can be used as a predictor of outcome (e.g. Hepatitis C)

Natural History

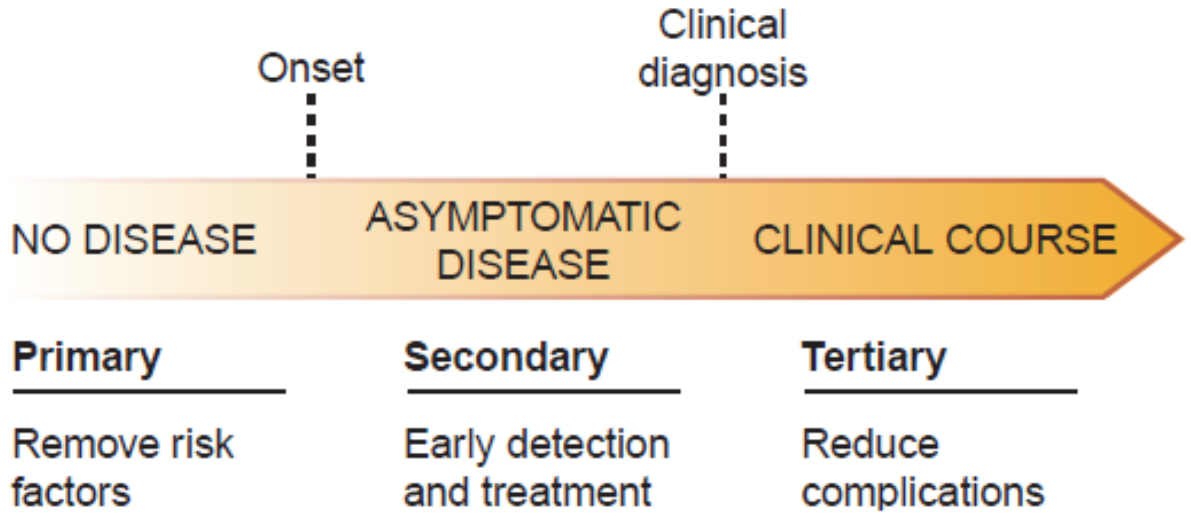
- *Prognosis* refers to the probable outcome and prospect of recovery from a disease.
- It can be designated as chances for full recovery, possibility of complications, or anticipated survival time.
- Prognosis often is presented in relation to treatment options, that is, the expected outcomes or chances for survival with or without a certain type of treatment.
- The prognosis associated with a given type of treatment usually is presented along with the risk associated with the treatment.

Preventing Disease



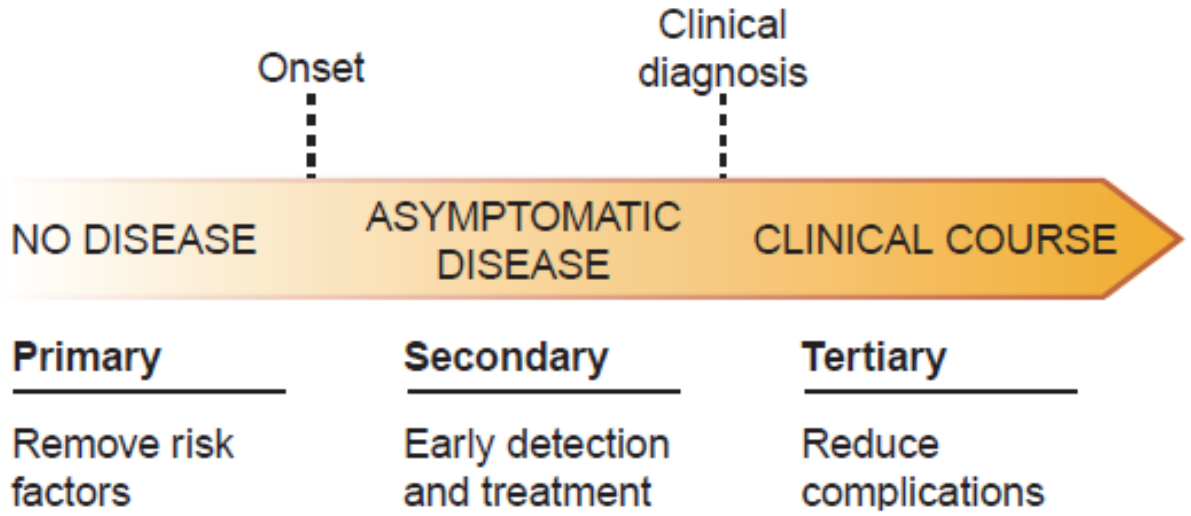
- *Primary prevention* is directed at keeping disease from occurring by removing all risk factors.
  - the administration of folic acid to pregnant women and women who may become pregnant to prevent fetal neural tube defects,
  - giving immunizations to children to prevent communicable disease,
  - counseling people to adopt healthy lifestyles as a means of preventing heart disease.
  - wearing seat belts in automobiles and helmet use on motorcycles

Preventing Disease



- *Secondary prevention* detects disease early when it is still asymptomatic and treatment measures can effect a cure or stop the disease from progressing.
  - The use of a Papanicolaou (Pap) smear for early detection of cervical cancer
  - History taking (asking if a person smokes), PE (blood pressure measurement), laboratory tests (cholesterol level determination), and other procedures (colonoscopy)
  - Most secondary prevention is done in clinical settings. All types of health care professionals (e.g., physicians, nurses, dentists, audiologists, optometrists) participate in secondary prevention.

Preventing Disease



- *Tertiary prevention* is directed at clinical interventions that prevent further deterioration or reduce the complications of a disease once it has been diagnosed.
  - The use of β-adrenergic drugs to reduce the risk of death in people who have had a heart attack.
- The boundaries of tertiary prevention go beyond treating the problem with which the person presents.
  - In people with diabetes, for example, tertiary prevention requires more than good glucose control. It also includes provision for regular ophthalmologic examinations for early detection of retinopathy, education for good foot care, and treatment for other cardiovascular risk factors such as hyperlipidemia.

Evidence-Based Practice and Practice Guidelines

- *Evidence-based practice* refers to making decisions in health care based on scientific data that has shown a specific way of managing a disease, patient symptoms, and complaints.
- Using evidence-based practice mandates that health care providers cannot practice according to only "their" way or according to "how it has always been done before."
- *Clinical practice guidelines* are systematically developed statements intended to inform practitioners and people in making decisions about health care for specific clinical circumstances.

2

Disorders of Integrative Function

HOMEOSTASIS

STRESS AND ADAPTATION

DISORDERS OF THE STRESS RESPONSE

HOMEOSTASIS

Constancy of the Internal Environment

Control Systems

Feedback Systems

Homeostasis

- *Stress* has become an increasingly discussed topic in today's world. The concept is discussed extensively in the health care fields and is found in economics, political science, business, and education.
- In the popular press, the physiologic response to stress is often implicated as a contributor to a variety of individual physical and mental challenges and societal problems.
- The concepts of stress and adaptation have their origin in the complexity of the human body and the interactions between the body cells and its many organ systems. These interactions require that a level of *homeostasis* or constancy be maintained during the many changes that occur in the internal and external environments.
- In effecting a state of constancy, homeostasis requires *feedback control systems* that regulate cellular function and integrate the function of the different body systems.

Constancy of the Internal Environment

- The environment in which body cells live is not the external environment that surrounds the organism, but rather the local fluid environment that surrounds each cell which is called Extracellular Fluid (ECF).
- It is from this internal environment that body cells receive their nourishment, and it is into this fluid that they secrete their wastes.
- A multicellular organism is able to survive only as long as the composition of the internal environment is compatible with the survival needs of the individual cells.
- The concept of a stable internal environment (homeostasis) was achieved through a system of carefully coordinated physiologic processes that oppose changes to both internal and external disturbances.

Control Systems

- The ability of the body to function and maintain homeostasis depends on the thousands of physiologic *control systems* that regulate body function.
- Just like any control system, each stress response involves a sensor to detect the change, an integrator to sum all incoming data and compare it with "normal," and effector(s) to try to reverse the change.
  - a hiker's eyes (sensor) see a snake (stressor). Her cerebral cortex (integrator) determines that the snake is a threat, and activates the heart, respiratory muscles, and many other organs (effectors) to assist her escape.
  - negative physical and psychological experiences during the prenatal and childhood periods can impact one's adult health. So more complex control systems are needed, and sometimes the stress response cannot restore balance and homeostasis.

Feedback Systems

- Most control systems in the body operate by *negative feedback mechanisms*

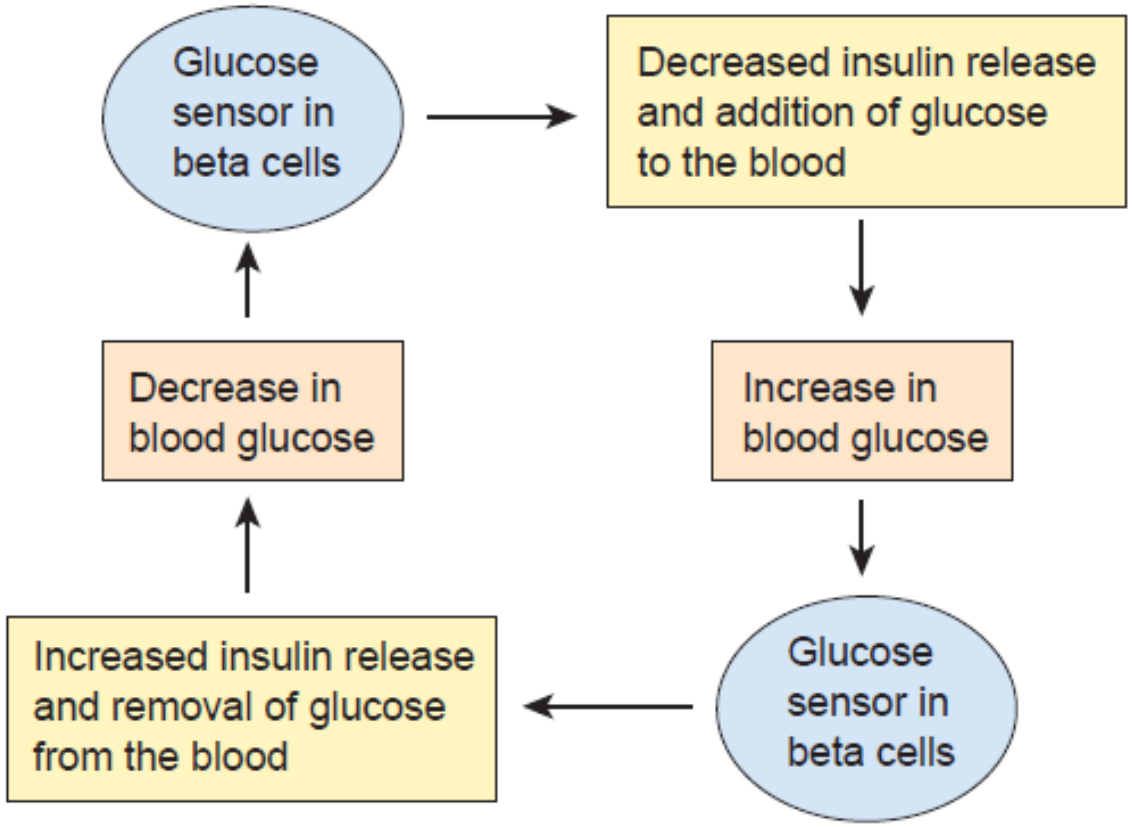


Illustration of negative feedback control mechanisms using blood glucose as an example.

STRESS AND ADAPTATION

The Stress Response

- Neuroendocrine Responses
- Immune Responses

Coping and Adaptation to Stress

- Adaptation
- Factors Affecting the Ability to Adapt

The Stress Response

- Hans Selye, an endocrinologist in early 1930's described stress as "a state manifested by a specific syndrome of the body developed in response to any stimuli that made an intense systemic demand on it"
- He observed, "whether a man suffers from a loss of blood, an infectious disease, or advanced cancer, he loses his appetite, his muscular strength, and his ambition to accomplish anything. Usually the patient also loses weight and even his facial expression betrays that he is ill.
- He assumed that the *hypothalamic–pituitary–adrenal (HPA)* axis played a pivotal role in the development of the stress response.

The Stress Response

- Selye labeled the response of the body to the stress as the *general adaptation syndrome (GAS)*
- the GAS involves three stages:
  - alarm stage, is characterized by a generalized stimulation of the sympathetic nervous system and the HPA axis, resulting in the release of catecholamines and cortisol.
  - During the resistance stage, the body selects the most effective and economic channels of defense. During this stage, the increased cortisol levels, which were present during the first stage, drop because they are no longer needed.
  - If the stressor is prolonged or overwhelms the ability of the body to defend itself, the exhaustion stage ensues, during which resources are depleted and signs of "wear and tear" or systemic damage appear.

Neuroendocrine Responses

- The manifestations of the stress response are strongly influenced by both the nervous and endocrine systems.
- The results of the coordinated release of the neuro-hormones include:
  - the mobilization of energy,
  - a sharpened focus and awareness,
  - increased cerebral blood flow and glucose utilization,
  - enhanced cardiovascular and respiratory functioning,
  - redistribution of blood flow to the brain and muscles,
  - modulation of the immune response,
  - inhibition of reproductive function,
  - decrease in appetite.

Neuroendocrine Responses

TABLE 9.1 HORMONES INVOLVED IN THE NEUROENDOCRINE RESPONSES TO STRESS

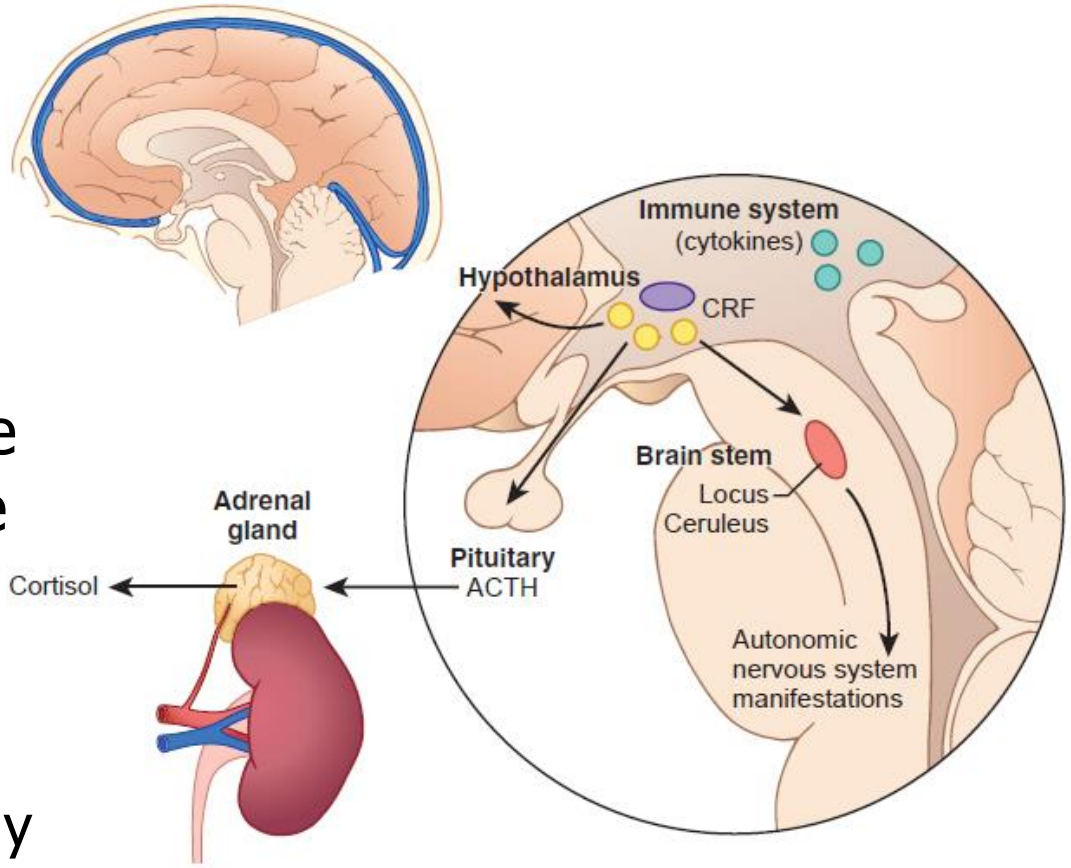
HORMONES ASSOCIATED WITH THE STRESS RESPONSE	SOURCE OF THE HORMONE	PHYSIOLOGIC EFFECTS
Catecholamines (NE, epinephrine)	LC, adrenal medulla	Produces a decrease in insulin release and an increase in glucagon release resulting in increased glycogenolysis, gluconeogenesis, lipolysis, proteolysis, and decreased glucose uptake by the peripheral tissues; an increase in heart rate, cardiac contractility, and vascular smooth muscle contraction; and relaxation of bronchial smooth muscle
Corticotropin-releasing factor (CRF)	Hypothalamus	Stimulates ACTH release from the anterior pituitary and increased activity of the LC neurons
Adrenocorticotropic hormone (ACTH)	Anterior pituitary	Stimulates the synthesis and release of cortisol
Glucocorticoid hormones (*e.g.*, cortisol)	Adrenal cortex	Potentiates the actions of epinephrine and glucagon; inhibits the release and/or actions of the reproductive hormones and thyroid-stimulating hormone; and produces a decrease in immune cells and inflammatory mediators
Mineralocorticoid hormones (*e.g.*, aldosterone)	Adrenal cortex	Increases sodium absorption by the kidney
Antidiuretic hormone (ADH, vasopressin)	Hypothalamus, posterior pituitary	Increases water absorption by the kidney; produces vasoconstriction of blood vessels; and stimulates the release of ACTH

Immune Responses

- Immune cells such as monocytes and lymphocytes can penetrate the blood–brain barrier and take up residence in the brain, where they secrete chemical messengers called cytokines that influence the stress response.
- the immune and neuroendocrine systems share common signal pathways (i.e., messenger molecules and receptors), that hormones and neuropeptides can alter the function of immune cells, and that the immune system and its mediators can modulate neuroendocrine function.
- Receptors for a number of CNS-controlled hormones and neuromediators reportedly have been found on lymphocytes.
  - glucocorticoids, insulin, testosterone, prolactin, catecholamines, estrogens, acetylcholine, and growth hormone have receptors on lymphocytes suggesting that these hormones and neuromediators influence lymphocyte function. (e.g. cortisol and suppress the immune system)

Immune Responses

- It has been observed that the HPA axis is activated by cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor (TNF) that are released from immune cells.
- A second possible route for neuroendocrine regulation of immune function is through the sympathetic nervous system and the release of catecholamines
  - Centrally acting CRF activates the ANS through multisynaptic descending pathways, and circulating epinephrine acts synergistically with CRF and cortisol to inhibit the function of the immune system.



Coping and Adaptation to Stress

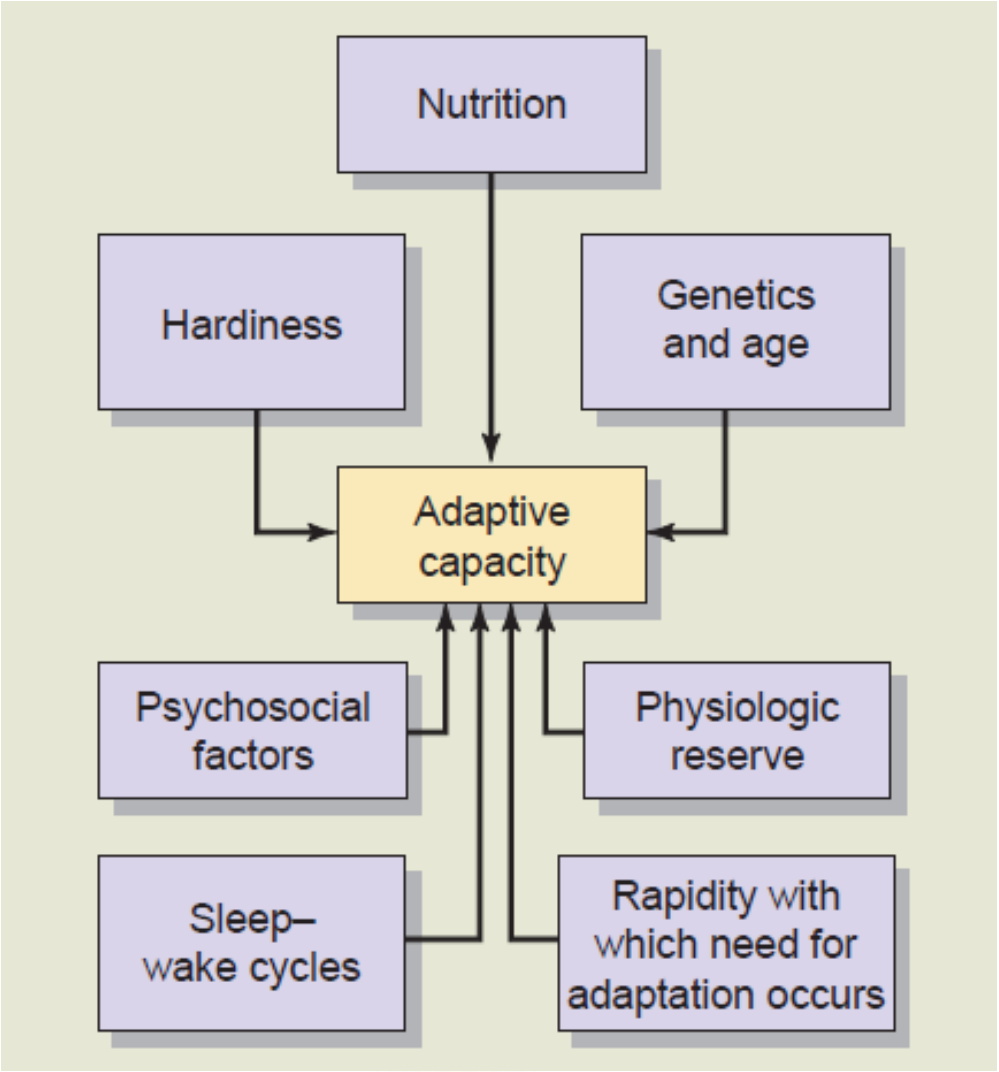
- The ability to adapt to a wide range of environments and stressors is not peculiar to humans and is found throughout life.
- The higher the organism is on the evolutionary scale, the larger its repertoire of adaptive mechanisms and its ability to select and limit aspects of the environment to which it responds.
- The most fully evolved mechanisms are the social responses through which people or groups modify their environments, their habits, or both to achieve a way of life that is best suited to their needs.

Adaptation

- Human beings, because of their highly developed nervous system and intellect, usually have alternative mechanisms for adapting and have the ability to control many aspects of their environment.
  - Air conditioning
  - Antiseptic agents
  - Immunizations
- At the same time, modern technology creates new challenges for adaptation and provides new sources of stress
  - Noise
  - Air polloution
  - increased exposure to harmful chemicals
  - changes in biologic rhythms imposed by shift work and global travel.

Factors Affecting the Ability to Adapt

- *Adaptation* implies that an individual has successfully created a new balance between the stressor and the ability to deal with it.
- The means used to attain this balance are called *coping strategies* or *coping mechanisms*.
- Coping mechanisms are the emotional and behavioral responses used to manage threats to our physiologic and psychological homeostasis.



Factors Affecting the Ability to Adapt

Physiologic and Anatomic Reserve

- The ability of body systems to increase their function given the need to adapt is known as the physiologic reserve.
  - The red blood cells carry more oxygen than the tissues can use, the liver and fat cells store excess nutrients, and bone tissue stores calcium in excess of that needed for normal neuromuscular function.
  - Many of the body organs, such as the lungs, kidneys, and adrenals, are paired to provide anatomic reserve as well.

Factors Affecting the Ability to Adapt

Time

- Adaptation is most efficient when changes occur gradually rather than suddenly.
  - It is possible, for instance, to lose a liter or more of blood through chronic gastrointestinal bleeding over a week without manifesting signs of shock. However, a sudden hemorrhage that causes rapid loss of an equal amount of blood is likely to cause hypotension and shock.

Factors Affecting the Ability to Adapt

Genetics

- Genetics can ensure that the systems that are essential to adaptation function adequately. Even a gene that has deleterious effects may prove adaptive in some environments.
  - In Africa, the gene for sickle cell anemia persists in some populations because it provides some resistance to infection with the parasite that causes malaria

Age

- The capacity to adapt is decreased at the extremes of age. The ability to adapt is impaired by the immaturity of an infant, much as it is by the decline in functional reserve that occurs with age.
  - Difficulty in concentrating urine in infants and elderly people.

Factors Affecting the Ability to Adapt

Gender

- It has been hypothesized that sex hormones are the basis of biologic differences in cardiovascular, respiratory, endocrine, renal, and neurophysiologic function between males and females.
- Technological advances in cellular and molecular biology have shown that there are fundamental differences in the locale and regulation of individual genes in the male and female genome.
- In this regard there are differences in the physiologic stress response in both the HPA axis and in the ANS.
- Gender-based differences in activation of the stress response may partially explain differences in susceptibility to diseases in which the stress response may play a causal role.

Factors Affecting the Ability to Adapt

Health Status

- Physical and mental health status determines physiologic and psychological reserves and is a strong determinant of the ability to adapt.
  - Severe emotional stress often produces disruption of physiologic function and limits the ability to make appropriate choices related to long-term adaptive needs.

Nutrition

- There are 50 to 60 essential nutrients, including minerals, lipids, certain fatty acids, vitamins, and specific amino acids. Deficiencies or excesses of any of these nutrients can alter a person's health status and impair the ability to adapt.
  - Obesity and alcohol abuse

Factors Affecting the Ability to Adapt

Sleep–Wake Cycles

- Sleep is considered to be a restorative function in which energy is restored and tissues are regenerated.
- Sleep occurs in a cyclic manner, alternating with periods of wakefulness and increased energy use.
- Biologic rhythms play an important role in adaptation to stress, development of illness, and response to medical treatment.
  - Insomnia, increased somnolence
  - Acute stress, loss of a loved one, recovery from surgery, pain Air travel and jet lag are common causes of transient and short-term insomnia and sleep disorders.

Factors Affecting the Ability to Adapt

Hardiness

- the concept of hardiness describes a personality characteristic that includes a sense of having control over the environment, a sense of having a purpose in life, and an ability to conceptualize stressors as a challenge rather than a threat.
- Many studies by nurses and social psychologists suggest that hardiness is correlated with positive health outcomes.

Factors Affecting the Ability to Adapt

Psychosocial Factors

- Several studies have related social factors and life events to illness.
- Scientific interest in the social environment as a cause of stress has gradually broadened to include the social environment as a resource that modulates the relation between stress and health.
- Presumably, people who can mobilize strong supportive resources from within their social relationships are better able to withstand the negative effects of stress on their health.
- Close relationships with others can involve positive effects as well as the potential for conflict and may, in some situations, leave the person less able to cope with life stressors.

DISORDERS OF THE STRESS RESPONSE

Effects of Acute Stress

Effects of Chronic Stress

Posttraumatic Stress Disorder

Treatment of Stress Disorders

Disorders of the stress response

- For the most part, the stress response is meant to be acute and time limited. The time-limited nature of the process renders the accompanying catabolic and immunosuppressive effects advantageous. It is the chronicity of the response that is thought to be disruptive to physical and mental health.
- Patterns of stressors in relation to time:
  - Acute time-limited: Occurs over a short time and does not recur.
  - Chronic intermittent or sustained: The patient is chronically exposed to the stressor.
- Chronic exposure to a stressor can fatigue the system and impair its effectiveness.

Effects of Acute Stress

- The reactions to acute stress are those associated with the ANS, the fight-or-flight response.
- The manifestations of the stress response:
  - pounding headache; a cold, moist skin; a stiff neck
  - Increased HR, RR, sweating, rising blood pressure, . . .
- Increased alertness and cognitive functioning enable rapid processing of information and arrival at the most appropriate solution to the threatening situation.
- However, for people with limited coping abilities, either because of physical or mental health, the acute stress response may be detrimental

Effects of Acute Stress

TABLE 9.2 POSSIBLE STRESS-INDUCED HEALTH PROBLEMS

- Mood disorders
- Anxiety
- Depression
- PTSD
- Eating disorders
- Sleep disorders
- Diabetes type 2
- Hypertension
- Infection
- Exacerbation of autoimmune disorders
- Gastrointestinal problems
- Pain
- Obesity
- Eczema
- Cancer
- Atherosclerosis
- Migraine

Effects of Chronic Stress

- The stress response is designed to be an acute self-limited response in which activation of the ANS and the HPA axis is controlled in a negative feedback manner.
- Chronicity and excessive activation of the stress response can result from chronic illnesses as well as contribute to the development of long-term health problems.
  - Stress is linked to health disorders, such as diseases of the cardiovascular, gastrointestinal, immune, and neurologic systems, as well as depression, chronic alcoholism and drug abuse, eating disorders, accidents, and suicide.

Posttraumatic Stress Disorder

- Posttraumatic stress disorder (PTSD) is characterized by a severe stress response secondary to experiencing previous trauma.
- Although war is a significant cause of PTSD, other major catastrophic events, such as weather-related disasters (hurricanes, earthquakes, and floods), airplane crashes, terrorist bombings, and rape or child abuse, also may result in development of the disorder.
- People who are exposed to PTSD are also at risk for development of:
  - major depression, panic disorder, generalized anxiety disorder, and substance abuse.
  - They may also have physical symptoms and illnesses (e.g., hypertension, asthma, and chronic pain syndromes).

Posttraumatic Stress Disorder

- PTSD is characterized by a variety of symptoms that are experienced as states of intrusion, avoidance, and hyperarousal.
- ***Intrusion*** refers to the occurrence of "flashbacks" during waking hours or nightmares in which the past traumatic event is relived, often in vivid and frightening detail.
- ***Avoidance*** refers to the emotional numbing that accompanies this disorder and disrupts important personal relationships.
  - Because a person with PTSD has not been able to resolve the painful feelings associated with the trauma, depression is commonly a part of the clinical picture. Survivor guilt also may be a product of traumatic situations in which the person survived the disaster but loved ones did not.
- ***Hyperarousal*** refers to the presence of increased irritability, difficulty concentrating, an exaggerated startle reflex, and increased vigilance and concern over safety.
- In addition, memory problems, sleep disturbances, and excessive anxiety are commonly experienced by people with PTSD.

Posttraumatic Stress Disorder

- The triad of symptoms of intrusion, avoidance, and hyperarousal that characterize PTSD must be present together for at least 1 month, and the disorder must have caused clinically significant distress.
- Recent neuroanatomic studies have identified alterations in two brain structures (the amygdala and hippocampus).
  - fMRI imaging have shown increased reactivity of the amygdala and hippocampus and decreased reactivity of the anterior cingulate and orbitofrontal areas (involve in fear responses and memory).
- People with PTSD demonstrate decreased cortisol levels, increased sensitivity of cortisol receptors,
  - Therefore, persons with PTSD do not exhibit a classic stress response as described by Selye.

Treatment of Stress Disorders

- The treatment of stress should be directed toward helping people avoid coping behaviors that impose a risk to their health and providing them with alternative stress-reducing strategies.
  - producing a generalized decrease in sympathetic system activity and musculoskeletal tension.
- ***Relaxation:*** Progressive muscle relaxation is one method of relieving tension. Tension can be defined physiologically as the inappropriate contraction of muscle fibers.
  - systematic contraction and relaxation of major muscle groups.
  - As the person learns to relax, the various muscle groups are combined.
  - Eventually, the person learns to relax individual muscle groups without first contracting them.

Treatment of Stress Disorders

- ***Music Therapy:*** is used for both its physiologic and psychological effects. It involves listening to selected pieces of music as a means of ameliorating anxiety or stress, reducing pain, decreasing feelings of loneliness and isolation, buffering noise, and facilitating expression of emotion. Music usually is selected based on a person's musical preference and past experiences with music.
- ***Imagery:*** Guided imagery is another technique that can be used to achieve relaxation. One method is scene visualization, in which the person is asked to sit back, close the eyes, and concentrate on a scene narrated by the therapist. Whenever possible, all five senses are involved. The person attempts to see, feel, hear, smell, and taste aspects of the visual experience. Other types of imagery involve imagining the appearance of each of the major muscle groups and how they feel during tension and relaxation.

Treatment of Stress Disorders

- ***Biofeedback:*** is a technique in which a person learns to control physiologic functioning. It involves electronic monitoring of one or more physiologic responses to stress with immediate feedback of the specific response to the person undergoing treatment.

3

Mechanisms of Infectious Disease

INFECTIOUS DISEASES

MECHANISMS OF INFECTION

DIAGNOSIS AND TREATMENT OF INFECTIOUS DISEASES

Infectious Diseases

Terminology
Agents of Infectious Disease

Terminology

- ***Host***: Any organism capable of supporting the nutritional and physical growth requirements of another is called a host.
- ***Infection:*** describes the presence and multiplication within a host of another living organism, with subsequent injury to the host
- ***Colonization:*** describes the act of establishing a presence, a step required in the multifaceted process of infection.
- The internal and external exposed surfaces of the human body are normally and harmlessly inhabited by a multitude of bacteria, collectively referred to as the ***normal microflora***.
- ***Mutualism:*** is applied to an interaction in which the microorganism and the host both derive benefits from the interaction.
  - An interaction such as this is called ***commensalism***, and the colonizing microorganisms are sometimes referred to as ***commensal flora***.

Terminology

- A ***parasitic relationship*** is one in which only the infecting organism benefits from the relationship and the host either gains nothing from the relationship or sustains injury from the interaction.
- If the host sustains injury or pathologic damage in response to a parasitic infection, the process is called an ***infectious disease.***
- ***Virulence:*** is the disease-producing potential of the microorganism.
- ***Pathogens*** are virulent microorganisms that are usually found in diseases.
  - ***Harmless saprophytes***, are freeliving organisms obtaining their growth from dead or decaying organic material in the environment.
  - All microorganisms, can become ***opportunistic pathogens***, capable of producing an infectious disease when the health and immunity of the host have been severely weakened by illness, malnutrition, or medical therapy.

TABLE 12.1 COMMON PATHOGENS

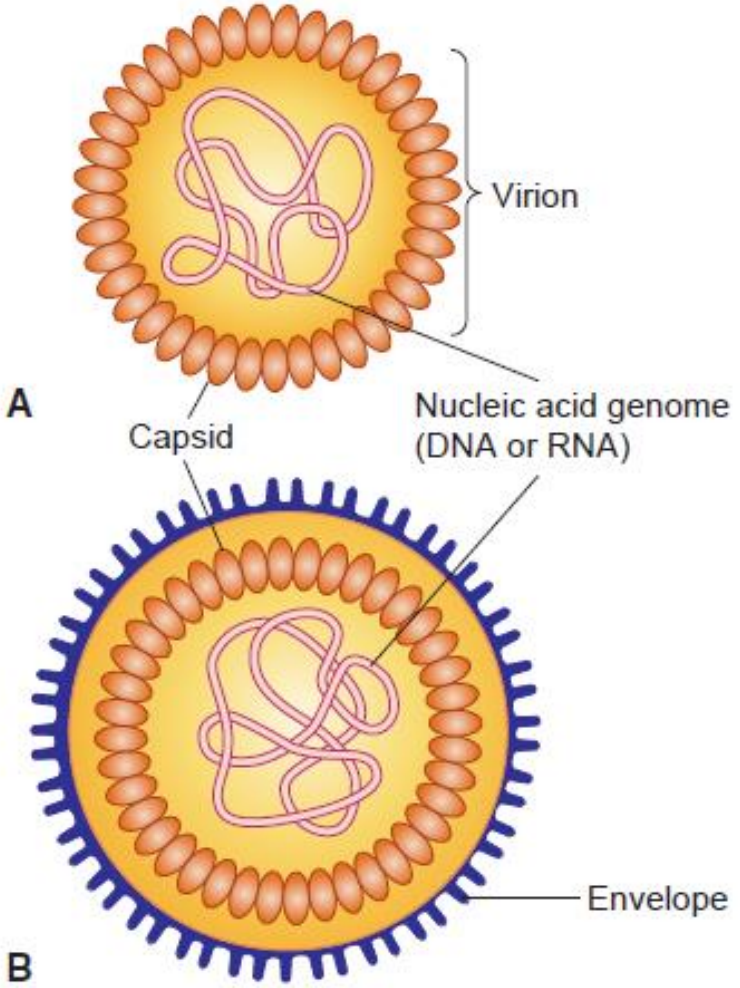
PATHOGEN	STRUCTURAL CHARACTERISTICS	FUNCTIONAL CHARACTERISTICS	TREATMENT	COMMON DISEASES
 Viruses	DNA/RNA and protein coat	Cannot reproduce outside of cells	Antivirals, which slow viral replication	Influenza, the common cold, measles, HIV/AIDS
 Bacteria	Microscopic cell without nucleus	Common on keyboards, water fountains, toilets …	Antibiotics, which slow bacterial reproduction	Strep throat, some sinus and lung infections, some food poisoning
 Fungi	Microscopic, unicellular (yeasts) or multicellular (molds)	Usually infect body surfaces and openings	Antifungals, which destroy the cell walls	Athlete's foot, yeast infections
 Protozoa	Microscopic, unicellular	Common in water supplies of developing countries	Antiprotozoan drugs, which interfere with protozoan metabolism	Malaria, sleeping sickness
 Worms	Multicellular	Prefer to live within body spaces and cells	Antihelminthics, which interfere with the worm's metabolism	Roundworms, tapeworms (helminths)

Agents of Infectious Disease

- ***Prions:*** Prions, protein particles that lack any kind of a demonstrable genome, are able to transmit infection.
  - A number of prion-associated diseases have been identified, including Creutzfeldt-Jakob disease and kuru in humans, scrapie in sheep, chronic wasting disease in deer and elk, and bovine spongiform encephalopathy (BSE or mad cow disease) in cattle.
- ***Viruses:*** Viruses are the smallest obligate intracellular pathogens. They have no organized cellular structures but instead consist of a protein coat, or capsid, surrounding a nucleic acid core, or genome, of RNA or DNA—never both.

Agents of Infectious Disease

- Some viruses are enclosed within a lipoprotein envelope derived from the cytoplasmic membrane of the parasitized host cell.
- Enveloped viruses include members of the herpesvirus group and paramyxoviruses (e.g., influenza and poxviruses). Certain enveloped viruses are continuously shed from the infected cell surface enveloped in buds pinched from the cell membrane.

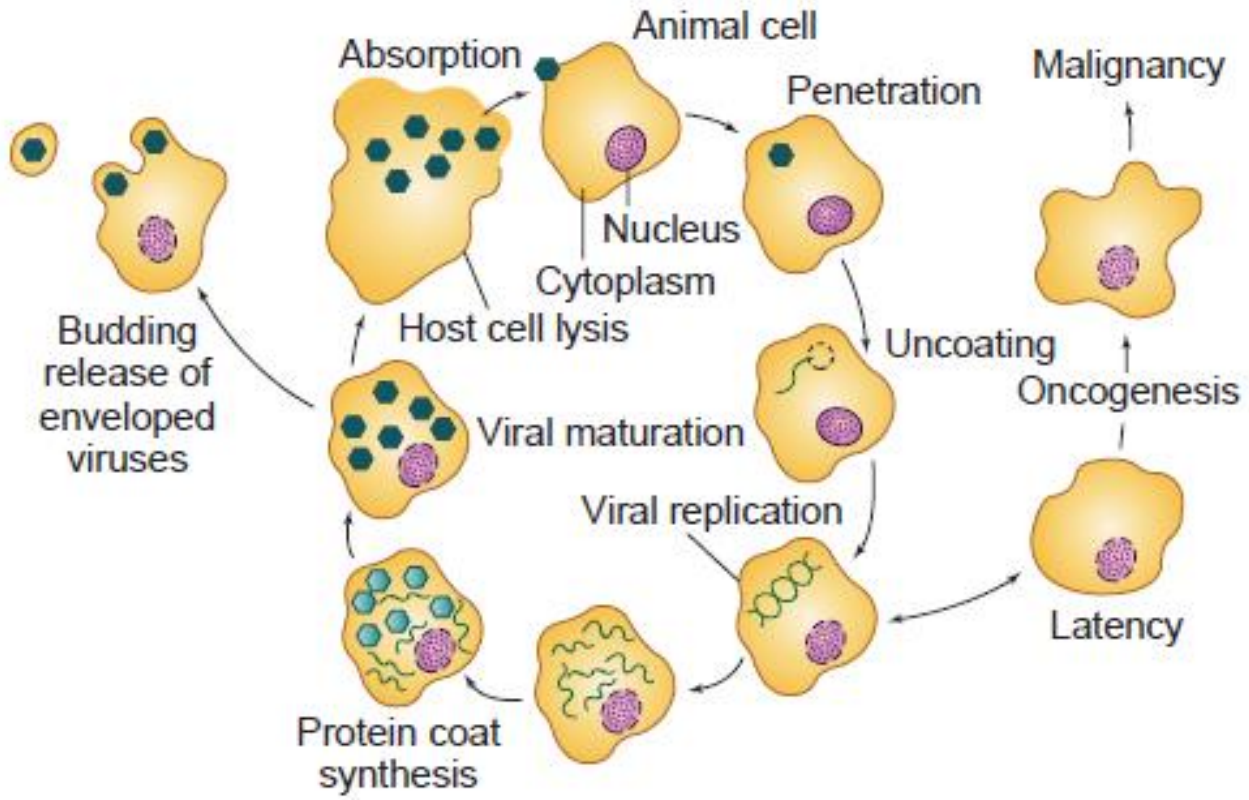


Agents of Infectious Disease

- Viruses are incapable of replication outside of a living cell. They must penetrate a susceptible living cell and use the biosynthetic structure of the cell to produce viral progeny.
- Not every viral agent causes lysis and death of the host cell during the course of replication. Some viruses enter the host cell and insert their genome into the host cell chromosome, where it remains in a latent, nonreplicating state for long periods without causing disease. Under the appropriate stimulation the virus undergoes active replication and produces symptoms of disease months to years later.

Agents of Infectious Disease

- Schematic representation of the many possible consequences of viral infection of host cells, including cell lysis (poliovirus), continuous release of budding viral particles, or latency (herpesviruses) and oncogenesis (papovaviruses)



Agents of Infectious Disease

- ***Bacteria:*** Bacteria are autonomously replicating unicellular organisms known as prokaryotes because they lack an organized nucleus.
- Compared with nucleated eukaryotic cells, the bacterial cell is small and structurally relatively primitive.
- Similar to eukaryotic cells, but unlike viruses, bacteria contain both DNA and RNA. They are the smallest of all living cells and range from 0.1 to 10 μm.
- They contain no organized intracellular organelles, the genome consists of only a single chromosome of DNA.
- Many bacteria transiently harbor smaller extrachromosomal pieces of circular DNA called plasmids. Occasionally, plasmids contain genetic information that increases the virulence or antibiotic resistance of the organism.

Agents of Infectious Disease

- Most bacteria produce a cell wall composed of a distinctive polymer known as peptidoglycan. Several bacteria synthesize an extracellular capsule composed of protein or carbohydrate. The capsule protects the organism from environmental hazards such as the immunologic defenses of the host.
- Certain bacteria are motile as the result of external whiplike appendages called flagella.
- Bacteria can also produce hairlike structures projecting from the cell surface called pili or fimbriae, which enable the organism to adhere to surfaces such as mucous membranes or other bacteria.

Agents of Infectious Disease

- Some bacteria produce pigments that give colonies a unique color; some produce highly resistant spores when faced with an unfavorable environment. The spores can exist in a quiescent state almost indefinitely until suitable growth conditions are encountered, at which time the spores germinate and the organism resumes normal metabolism and replication.
- Bacteria are designated as gram-positive organisms if they are stained purple by a primary basic dye (usually crystal violet). Those that are not stained by the crystal violet but are counterstained red by a second dye (safranin) are called gram-negative organisms.
- Another means of classifying bacteria according to microscopic staining properties is the acid-fast stain. These organisms are termed acid-fast and include a number of significant human pathogens, most notably Mycobacterium tuberculosis and other mycobacteria.

Agents of Infectious Disease

Rickettsiaceae, Anaplasmataceae, Chlamydiaceae, and Coxiella

- This interesting group of organisms combines the characteristics of viral and bacterial agents to produce disease in humans. All are obligate intracellular pathogens, like the viruses, but produce a rigid peptidoglycan cell wall, reproduce asexually by cellular division, and contain RNA and DNA, similar to the bacteria
- The *Rickettsiaceae* depend on the host cell for essential vitamins and nutrients. They infect but do not produce disease in the cells of certain arthropods such as fleas, ticks, and lice.9 The organisms are accidentally transmitted to humans through the bite of the arthropod (i.e., the vector) and produce a number of potentially lethal diseases, including Rocky Mountain spotted fever and epidemic typhus.

Agents of Infectious Disease

- The *Chlamydiaceae* appear to scavenge intermediates of energy metabolism such as adenosine triphosphate (ATP). They are slightly smaller than the Rickettsiaceae but are structurally similar and are transmitted directly between susceptible vertebrates without an intermediate arthropod host.
- Organisms within the family *Anaplasmataceae* (including the reorganized genera Ehrlichia, Anaplasma, Neorickettsia, and Wolbachia) are also obligate intracellular organisms that resemble the Rickettsiaceae in structure and produce a variety of veterinary and human diseases, some of which have a tick vector.

Agents of Infectious Disease

- The genus *Coxiella* contains only one species, C. burnetii. Like its rickettsial counterparts, it is a gram-negative intracellular organism that infects a variety of animals, including cattle, sheep, and goats.12 In humans, Coxiella infection produces a disease called Q fever, characterized by a nonspecific febrile illness often accompanied by headache, chills, and mild pneumonia-like symptoms
- The organism produces a highly resistant sporelike stage that is transmitted to humans when contaminated animal tissue is aerosolized (e.g., during meat processing) or by ingestion of contaminated milk.

Agents of Infectious Disease

- ***Fungi:*** The fungi are free-living, eukaryotic saprophytes found in every habitat on earth. Some are members of the normal human microflora.
- Fortunately, few fungi are capable of causing diseases in humans, and most of these are incidental, selflimited infections of skin and subcutaneous tissue.
- Serious fungal infections are rare and usually initiated through puncture wounds or inhalation. Despite their normally harmless nature, fungi can cause life-threatening opportunistic diseases when host defense capabilities have been disabled.

Agents of Infectious Disease

- The fungi can be separated into two groups, *yeasts* and molds, based on rudimentary differences in their morphology.
  - The yeasts are single-celled organisms, approximately the size of red blood cells, which reproduce by a budding process. The buds separate from the parent cell and mature into identical daughter cells.
  - Molds produce long, hollow, branching filaments called hyphae. Some molds produce cross walls, which segregate the hyphae into compartments, and others do not.
  - Colonies of yeast are generally smooth with a waxy or creamy texture. Molds tend to produce cottony or powdery colonies composed of mats of hyphae collectively called a mycelium.

Agents of Infectious Disease

- ***Parasites:*** In a strict sense, any organism that derives benefits from its biologic relationship with another organism is a parasite. In the study of clinical microbiology, however, the term parasite has evolved to designate members of the animal kingdom that infect and cause disease in other animals, and includes protozoa, helminths, and arthropods.
- The *protozoa* are unicellular animals with a complete complement of eukaryotic cellular machinery, including a welldefined nucleus and organelles.
  - Protozoan infections can be passed directly from host to host such as through sexual contact, indirectly through contaminated water or food, or by way of an arthropod vector.
  - Direct or indirect transmission results from the ingestion of highly resistant cysts or spores that are shed in the feces of an infected host. When the cysts reach the intestine, they mature into vegetative forms called trophozoites, which are capable of asexual reproduction or cyst formation.

Agents of Infectious Disease

- The *helminths* are a collection of wormlike parasites that include the nematodes or roundworms, cestodes or tapeworms, and trematodes or flukes.
- The helminths reproduce sexually within the definitive host, and some require an intermediate host for the development and maturation of offspring.
- Humans can serve as the definitive or intermediate host and, in certain diseases such as trichinosis, as both. Transmission of helminth diseases occurs primarily through the ingestion of fertilized eggs (ova) or the penetration of infectious larval stages through the skin—directly or with the aid of an arthropod vector.

Agents of Infectious Disease

- The *parasitic arthropods* of humans and animals include the vectors of infectious diseases (e.g., ticks, mosquitoes, biting flies) and the ectoparasites.
- The *ectoparasites* infest external body surfaces and cause localized tissue damage or inflammation secondary to the bite or burrowing action of the arthropod.
- The most prominent human ectoparasites are mites (scabies), chiggers, lice (head, body, and pubic), and fleas.
- Many of the ectoparasites are vectors of other infectious diseases, including endemic typhus and bubonic plague (fleas) and epidemic typhus (lice).

Mechanisms of Infection

Epidemiology of Infectious Diseases

Portal of Entry

- Penetration
- Direct Contact
- Ingestion
- Inhalation

Source

Symptomatology

Disease Course

Site of Infection

Virulence Factors

Epidemiology of Infectious Diseases

- Epidemiology is the study of factors, events, and circumstances that influence the transmission of infectious diseases among humans.
- infectious diseases must be classified according to incidence, portal of entry, source, symptoms, disease course, site of infection, and virulence factors so that potential outbreaks may be predicted and averted or appropriately treated.

Epidemiology of Infectious Diseases

- The term *incidence* is used to describe the number of new cases of an infectious disease that occur within a defined population (e.g., per 100,000 people) over an established period of time (e.g., monthly, quarterly, yearly).
- Disease *prevalence* indicates the number of active cases at any given time.
- A disease is considered *endemic* in a particular geographic region if the incidence and prevalence are expected and relatively stable.
- An *epidemic* describes an abrupt and unexpected increase in the incidence of disease over endemic rates.
- A *pandemic* refers to the spread of disease beyond continental boundaries. The advent of rapid worldwide travel increased the likelihood of pandemic transmission of pathogenic microorganisms.

Portal of Entry

- The portal of entry refers to the process by which a pathogen enters the body, gains access to susceptible tissues, and causes disease.
- **Penetration**: Any disruption in the integrity of the body's surface barrier—skin or mucous membranes—is a potential site for invasion of microorganisms (abrasions, burns, or penetrating wounds; medical procedures such as surgery or catheterization).
- **Direct Contact**: Some pathogens are transmitted directly from infected tissue or secretions to exposed, intact mucous membranes.
  - STI infections (gonorrhea, syphilis, chlamydia, and genital herpes).
  - Vertical transmission leads to congenital infection.

Portal of Entry

- **Ingestion**: The entry of pathogenic microorganisms or their toxic products through the oral cavity and gastrointestinal tract represents one of the more efficient means of disease transmission in humans.
  - Many bacterial, viral, and parasitic infections, including cholera, typhoid fever, dysentery (amebic and bacillary), food poisoning, traveler's diarrhea, cryptosporidiosis, and hepatitis A, are initiated through the ingestion of contaminated food and water.
- **Inhalation**: The surface of the respiratory tree is lined with a layer of mucus that is continuously swept up and away from the lungs and toward the mouth by the beating motion of ciliated epithelial cells. a number of pathogens can invade the human body through the respiratory tract.
  - bacterial pneumonia (Streptococcus pneumoniae, L. pneumophila), meningitis (Neisseria meningitidis, Haemophilus influenzae), tuberculosis and . . .

Source

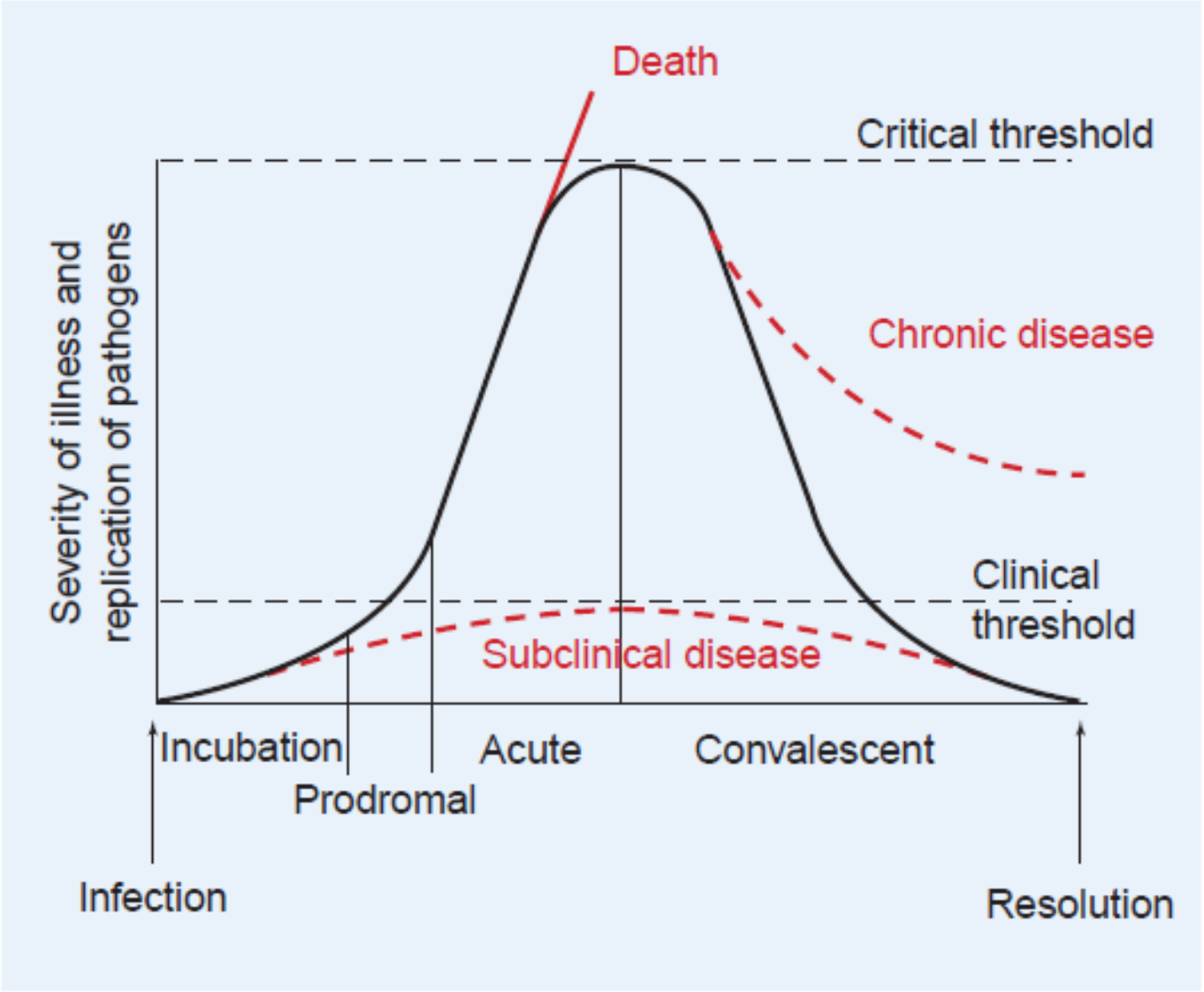
- The source of an infectious disease refers to the location, host, object, or substance from which the infectious agent was acquired: essentially the "who, what, where, and when" of disease transmission.
- The source may be *endogenous* (acquired from the host's own microbial flora, as would be the case in an opportunistic infection) or *exogenous* (acquired from sources in the external environment, such as the water, food, soil, or air).
- The source of the infectious agent can also be another human being, as from mother to child during gestation (congenital infections); an inanimate object; an animal; or a biting arthropod.
  - Inanimate objects that carry an infectious agent are known as fomites.
  - Zoonoses are a category of infectious diseases passed from other animal species to humans
  - feces, blood, body fluids, respiratory secretions, and urine.

Symptomatology

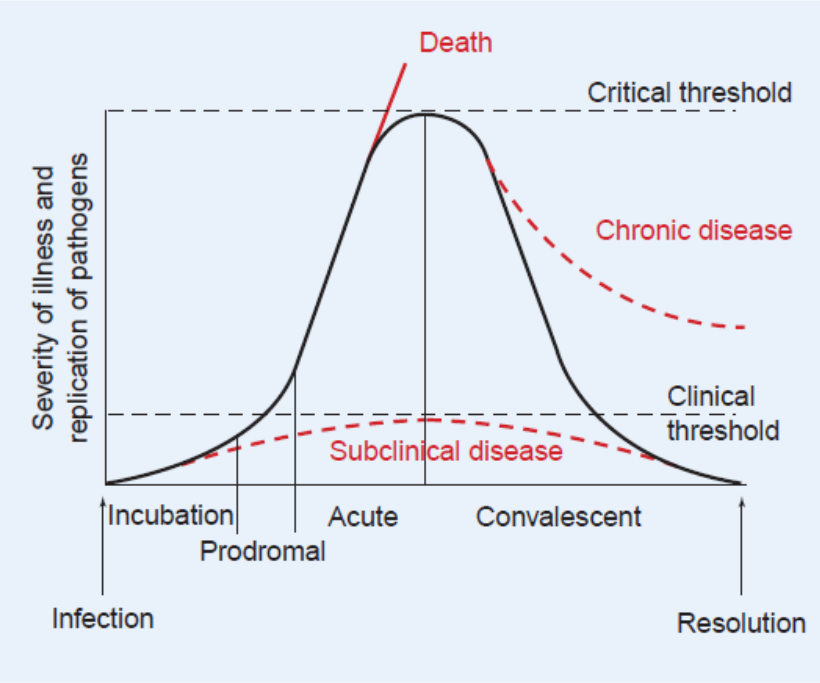
- The term *symptomatology* refers to the collection of signs and symptoms expressed by the host during the disease course. This is also known as the clinical picture, or disease presentation, and can be characteristic of any given infectious agent.
  - Specific and reflect the site of infection (e.g., diarrhea, rash, convulsions, hemorrhage, and pneumonia).
  - Nonspecific and can be shared by a number of diverse infectious diseases (e.g., fever, myalgia, headache, and lethargy).
  - Obvious, (e.g., chickenpox or measles).
  - Covert symptoms, such as an increased white blood cell count

Disease Course

- Stages of a primary infectious disease as they appear in relation to the severity of symptoms and numbers of infectious agents.
- The clinical threshold corresponds with the initial expression of recognizable symptoms, whereas the critical threshold represents the peak of disease intensity.

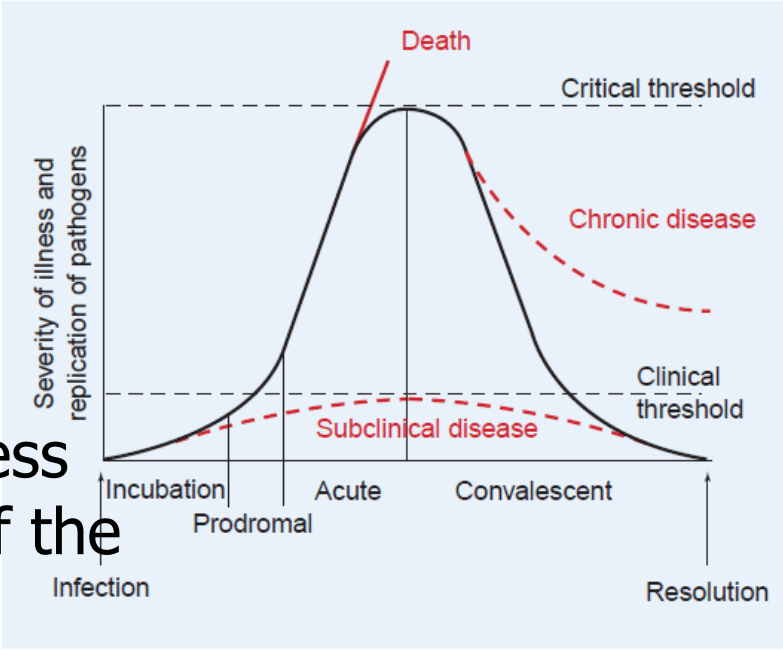


Disease Course



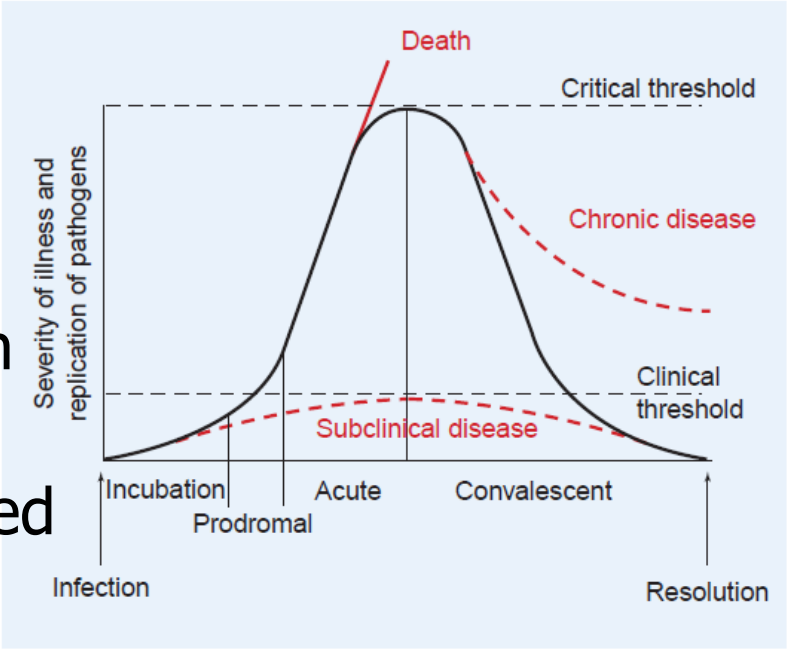
- The *incubation period* is the phase during which the pathogen begins active replication without producing recognizable symptoms in the host.
  - Short: e.g., salmonellosis (6 to 24 hours),
  - Prolonged: such as that of hepatitis B (50 to 180 days) or HIV (months to years).
- The *prodromal stage* is the initial appearance of symptoms in the host, although the clinical presentation during this time may be only a vague sense of malaise. The host may experience mild fever, myalgia, and fatigue.

Disease Course



- The *acute stage* is the period during which the host experiences the maximum impact of the infectious process corresponding to rapid proliferation and dissemination of the pathogen.
  - During this phase, toxic by-products of microbial metabolism, cell lysis, and the immune response mounted by the host combine to produce tissue damage and inflammation.
- The *convalescent period* is characterized by the containment of infection, progressive elimination of the pathogen, repair of damaged tissue, and resolution of associated symptoms.
- The *resolution* is the total elimination of a pathogen from the body without residual signs or symptoms of disease.

Disease Course



- Several notable exceptions to the classic presentation of an infectious process have been recognized.
- Chronic infectious diseases have a markedly protracted and sometimes irregular course.
  - The host may experience symptoms of the infectious process continuously or sporadically for months or years without a convalescent phase.
- In contrast, subclinical or subacute illness progresses from infection to resolution without clinically apparent symptoms.
- A disease is called insidious if the prodromal phase is protracted;
- a fulminant illness is characterized by abrupt onset of symptoms with little or no prodrome.
- Fatal infections are variants of the typical disease course.

Site of Infection

- The type of pathogen, the portal of entry, and the competence of the host's immunologic defense system ultimately determine the site of an infectious disease.
  - M. pneumoniae, influenza viruses, and L. pneumophila rarely cause disease outside the respiratory tract; infections caused by N. gonorrhoeae are generally confined to the genitourinary tract.
  - Helicobacter pylori is an extreme example of a site-specific pathogen.
- An abscess is a localized pocket of infection composed of devitalized tissue, microorganisms, and the host's phagocytic white blood cells.
- Infections of biomedical implants such as catheters, artificial heart valves, and prosthetic bone implants are seldom cured by the host's immune response and antimicrobial therapy. The infecting organism colonizes the surface of the implant, producing a dense matrix of cells, host proteins, and capsular material—a biofilm— necessitating the removal of the device.

Virulence Factors

Virulence factors are substances or products generated by infectious agents that enhance their ability to cause disease.

- ***Toxins*** are substances that alter or destroy the normal function of the host or host's cells. Bacterial toxins have a diverse spectrum of activity and can be divided into two main types: exotoxins and endotoxins.
  - *Exotoxins* are proteins released from the bacterial cell during growth. Bacterial exotoxins enzymatically inactivate or modify key cellular constituents, leading to cell death or dysfunction (Diphtheria, tetanus, cholera toxin , . . .)
  - Bacterial exotoxins that produce vomiting and diarrhea are sometimes referred to as enterotoxins.

Virulence Factors

- Endotoxins. In contrast to exotoxins, endotoxins do not contain protein, are not actively released from the bacterium during growth, and have no enzymatic activity. Rather, endotoxins are complex molecules composed of lipid and polysaccharides found in the cell wall of gram-negative bacteria.
- Studies of different endotoxins have indicated that the lipid portion of the endotoxin confers the toxic properties to the molecule.
- Endotoxins are potent activators of a number of regulatory systems in humans. A small amount of endotoxin in the circulatory system (endotoxemia) can induce clotting, bleeding, inflammation, hypotension, and fever. The sum of the physiologic reactions to endotoxins is sometimes called endotoxic shock

Adhesion Factors

- No interaction between microorganisms and humans can progress to infection or disease if the pathogen is unable to attach to and colonize the host.
- The process of microbial attachment may be site specific (e.g., mucous membranes, skin surfaces), cell specific (e.g., T lymphocytes, respiratory epithelium, intestinal epithelium), or nonspecific (e.g., moist areas, charged surfaces).
- The site to which microorganisms adhere is called a receptor, and the reciprocal molecule or substance that binds to the receptor is called a ligand or adhesin.
- Many viral agents, including influenza, mumps, measles, and adenovirus, produce filamentous appendages or spikes called hemagglutinins that recognize carbohydrate receptors on the surfaces of specific cells in the upper respiratory tract of the host.

Adhesion Factors

- **Evasive Factors**: A number of factors produced by microorganisms enhance virulence by evading various components of the host's immune system.
- Extracellular polysaccharides, including capsules, slime, and mucous layers, discourage engulfment and killing of pathogens by the host's phagocytic white blood cells (i.e., neutrophils and macrophages).
- Encapsulated organisms such as S. agalactiae, S. pneumoniae, N. meningitidis, and H. influenza type b (before the vaccine) are a cause of significant morbidity and mortality in neonates and children who lack protective anticapsular antibodies.
- Certain bacterial, fungal, and parasitic pathogens avoid phagocytosis by excreting leukocidin C toxins, which cause specific and lethal damage to the cell membrane of host neutrophils and macrophages.

Adhesion Factors

- Salmonellosis, listeriosis, and Legionnaire disease, are adapted to survive and reproduce within phagocytic white blood cells after ingestion, avoiding or neutralizing the usually lethal products contained within the lysosomes of the cell.
- Helicobacter pylori, the infectious cause of gastritis and gastric ulcers, produces a urease enzyme on its outer cell wall. The urease converts gastric urea into ammonia, thus neutralizing the acidic environment of the stomach and allowing the organism to survive in this hostile environment.
- Strains of S. aureus produce a surface protein (protein A) that immobilizes immunoglobulin G (IgG), holding the antigen-binding region harmlessly away from the organisms.

Adhesion Factors

- **Invasive Factors:** are products produced by infectious agents that facilitate the penetration of anatomic barriers and host tissue.
- Most invasive factors are enzymes capable of destroying cellular membranes (e.g., phospholipases), connective tissue (e.g., elastases, collagenases), intercellular matrices (e.g., hyaluronidase), and structural protein complexes (e.g., proteases).
- It is the combined effects of invasive factors, toxins, and antimicrobial and inflammatory substances released by host cells to counter infection that mediate the tissue damage and pathophysiology of infectious diseases.

Diagnosis and Treatment of Infectious Diseases

Diagnosis

- Culture
- Serology
- DNA and RNA Sequencing

Treatment

- Antimicrobial agents
  - Antibacterial agents
  - Antiviral agents
  - Antifungal agents
  - Antiparasitic agents
- Immunotherapy
- Surgical Intervention

Diagnosis

- The diagnosis of an infectious disease requires two criteria:
  - the recovery of a probable pathogen or evidence of its presence from the infected sites of a diseased host,
  - and accurate documentation of clinical signs and symptoms compatible with an infectious process.
- In the laboratory, the diagnosis of an infectious agent is accomplished using three basic techniques: culture, serology, or the detection of characteristic antigens, genomic sequences, or metabolites produced by the pathogen.

Culture

- Culture refers to the propagation of a microorganism outside of the body, usually on or in artificial growth media such as agar plates or broth.
- The specimen from the host is inoculated into broth or onto the surface of an agar plate, and the culture is placed in a controlled environment such as an incubator until the growth of microorganisms becomes detectable.
- In the case of a bacterial pathogen, identification is based on microscopic appearance and Gram stain reaction, shape, texture, and color (i.e., morphology) of the colonies and by a panel of biochemical reactions that fingerprint salient biochemical characteristics of the organism.

Culture

- Fungi and mycoplasmas are cultured in much the same way as bacteria, but with more reliance on microscopic and colonial morphology for identification.
- Chlamydiaceae, Rickettsiaceae, and all human viruses are obligate intracellular pathogens.
- the propagation of these agents in the laboratory requires the inoculation of eukaryotic cells grown in culture (cell cultures).
- When a virus infects and replicates within cultured eukaryotic cells, it produces pathologic changes in the appearance of the cell called the cytopathic effect (CPE).
- The diagnosis of parasitic infectious diseases has traditionally relied on microscopic or, in the case of worms, visible identification of organisms, cysts, or ova directly from infected patient specimens.

Serology

- Serology is an indirect means of identifying infectious agents by measuring serum antibodies in the diseased host.
- A tentative diagnosis can be made if the antibody level, also called antibody titer, against a specific pathogen rises during the acute phase of the disease and falls during convalescence.
- IgM-specific antibodies generally rise and fall during the acute phase of the disease, whereas the synthesis of the IgG class of antibodies increases during the acute phase and remains elevated until or beyond resolution.

Serology

- Antigen detection incorporates features of culture and serology but reduces to a fraction the time required for diagnosis.
- This method relies on purified antibodies to detect antigens of infectious agents in specimens obtained from the diseased host.
- The source of antibodies used for antigen detection can be animals immunized against a particular pathogen or hybridomas.
- Fusing normal antibody-producing spleen cells from an immunized animal with malignant myeloma cells creates hybridomas. The resulting hybrid synthesizes large quantities of antibody.
- An antibody produced by a hybridoma is called a monoclonal antibody and is highly specific for a single antigen and a single pathogen.

Serology

- In general, the three types of labels used for the detection of pathogens are fluorescent dyes, enzymes, and particles such as latex beads.
  - Fluorescent antibodies allow visualization of an infectious agent with the aid of fluorescence microscopy.
  - The enzyme is capable of converting a colorless compound into a colored substance, thereby permitting detection of antibody bound to an infectious agent without the use of a fluorescent microscope.
  - Particles coated with antibodies clump together, or agglutinate, when the appropriate antigen is present in a specimen. Particle agglutination is especially useful when examining infected body fluids such as urine, serum, or spinal fluid.

DNA and RNA Sequencing

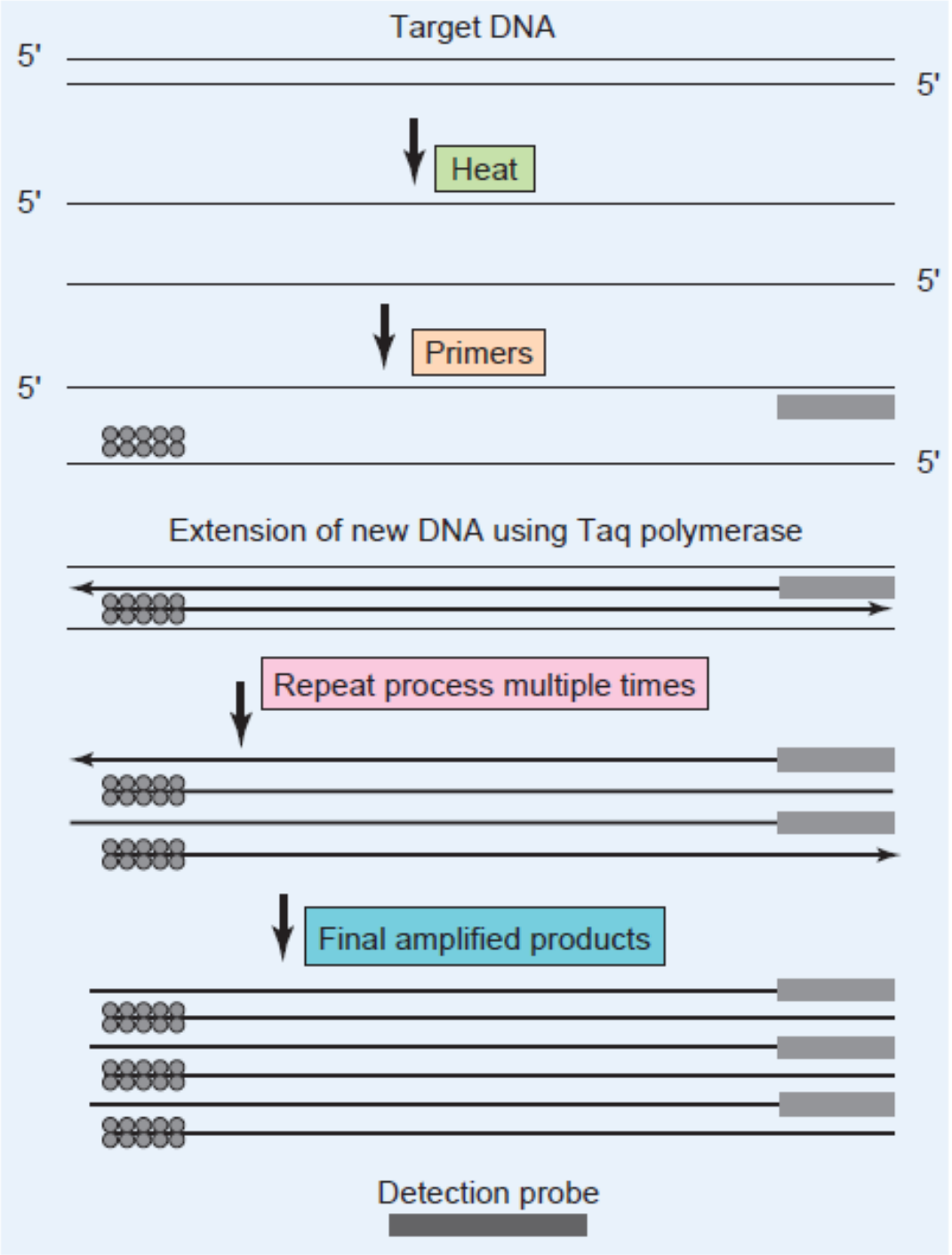
- DNA probe hybridization: Small fragments of DNA are cut from the genome of a specific pathogen and labeled with compounds (photoemitting chemicals or antigens) that allow detection.
- The labeled DNA probes are added to specimens from an infected host. If the pathogen is present, the probe attaches to the complementary strand of DNA on the genome of the infectious agent, permitting rapid diagnosis.
- Polymerase chain reaction (PCR): This method incorporates two unique reagents: a specific pair of oligonucleotides (usually less than 25 nucleotides long) called primers and a heat-stable DNA polymerase. To perform the assay, the primers are added to the specimen containing the suspect pathogen, and the sample is heated to melt the DNA in the specimen and then allowed to cool.

DNA and RNA Sequencing

- The primers locate and bind only to the complementary target DNA of the pathogen in question. The heat-stable polymerase begins to replicate the DNA from the point at which the primers attached, similar to two trains approaching one another on separate but converging tracks.
- After the initial cycle, DNA polymerization ceases at the point where the primers were located, producing a strand of DNA with a distinct size, depending on the distance separating the two primers.
- The specimen is heated again, and the process starts anew. After many cycles of heating, cooling, and polymerization, a large number of uniformly sized DNA fragments are produced only if the specific pathogen (or its DNA) is present in the specimen.
- The polymerized DNA fragments are separated by electrophoresis and visualized with a dye or identified by hybridization with a specific probe.

Polymerase chain reaction (PCR).

- The target DNA is first melted using heat (generally around 94°C) to separate the strands of DNA.
- Primers that recognize specific sequences in the target DNA are allowed to bind as the reaction cools. Using a unique, thermostable DNA polymerase called Taq and an abundance of deoxynucleoside triphosphates, new DNA strands are amplified from the point of the primer attachment.
- The process is repeated many times (called cycles) until millions of copies of DNA are produced, all of which have the same length defined by the distance (in base pairs) between the primer binding sites.
- These copies are then detected by electrophoresis and staining or through the use of labeled DNA probes that, similar to the primers, recognize a specific sequence located in the amplified section of DNA.



DNA and RNA Sequencing

- A modification of PCR, known as real-time PCR, continues to revolutionize medical diagnostics.
- Real-time PCR (RT-PCR) uses the same principles as PCR, but includes a fluorescencelabeled probe that specifically binds a target DNA sequence between the oligonucleotide primers.
- As the DNA is replicated by the DNA polymerase, the level of fluorescence in the reaction is measured. If fluorescence increases beyond a minimum threshold, the PCR is considered positive and indicates the presence of the target DNA in a specimen.
- Realtime PCR is very effective in determining the diagnosis of Clostridium difficile.

Treatment

- The goal of treatment for an infectious disease is complete removal of the pathogen from the host and the restoration of normal physiologic function to damaged tissues.
- Most infectious diseases of humans are self-limiting in that they require little or no medical therapy for a complete cure.
- When an infectious process gains the upper hand and therapeutic intervention is essential, the choice of treatment may medicinal through the use of antimicrobial agents; immunologic with antibody preparations, vaccines, or substances that stimulate and improve the host's immune function; or surgical by removing infected tissues.

Antimicrobial Agents

- **Antibacterial Agents.** Antibacterial agents are generally called antibiotics. Most antibiotics are actually produced by other microorganisms, primarily bacteria and fungi, as by-products of metabolism.
- Antibiotics usually are effective only against other prokaryotic organisms.
- An antibiotic is considered bactericidal if it causes irreversible and lethal damage to the bacterial pathogen and bacteriostatic if its inhibitory effects on bacterial growth are reversed when the agent is eliminated.
- Antibiotics can be classified into families of compounds with related chemical structure and activity

TABLE 12.4 CLASSIFICATION AND ACTIVITY OF ANTIBACTERIAL AGENTS (ANTIBIOTICS)

FAMILY	EXAMPLE	TARGET SITE	SIDE EFFECTS
Penicillins	Ampicillin	Cell wall	Allergic reactions
Cephalosporins	Cephalexin	Cell wall	Allergic reactions
Monobactams	Aztreonam	Cell wall	Rash
Carbapenem	Imipenem	Cell wall	Nausea, diarrhea
Aminoglycosides	Tobramycin	Ribosomes (protein synthesis)	Hearing loss Nephrotoxicity
Tetracyclines	Doxycycline	Ribosomes (protein synthesis)	Gastrointestinal irritation Allergic reactions Teeth and bone dysplasia
Macrolides	Clarithromycin	Ribosomes (protein synthesis)	Colitis Allergic reactions
Glycopeptides	Vancomycin	Ribosomes (protein synthesis)	Allergic reactions Hearing loss Nephrotoxicity
Quinolones	Ciprofloxacin	DNA synthesis	Gastrointestinal irritation, Tendon rupture
Miscellaneous	Chloramphenicol	Ribosomes (protein synthesis)	Anemia
	Rifampin	Ribosomes (protein synthesis)	Hepatotoxicity
	Trimethoprim	Folic acid synthesis	Allergic reactions Same as sulfonamides
Sulfonamides	Sulfadiazine	Folic acid synthesis	Allergic reactions Anemia Gastrointestinal irritation
Oxazolidinone	Linezolid	Ribosomes (protein synthesis)	Diarrhea, thrombocytopenia
Streptogramin	Quinupristin/dalfopristin	Ribosomes (protein synthesis)	Muscle and joint aches
Glycylcycline	Tigecycline	Ribosomes	Nausea, vomiting, diarrhea
Polymyxins	Colistin	Membrane	Confusion, visual disturbances, vertigo, kidney damage
Lipopeptide	Daptomycin	Membrane depolarization	Nausea, vomiting, constipation, diarrhea, headache

Antimicrobial Agents

- The four basic mechanisms of the antibiotic action include:
  - interference with a specific step in bacterial cell wall synthesis (e.g., penicillins, cephalosporins, glycopeptides, monobactams, carbapenems),
  - Inhibition of bacterial protein synthesis (e.g., aminoglycosides, macrolides, ketolides, tetracyclines, chloramphenicol, oxazolidinones, streptogramins, and rifampin),
  - interruption of nucleic acid synthesis (e.g., fluoroquinolones, nalidixic acid)
  - interference with normal metabolism (e.g., sulfonamides, trimethoprim)

Antimicrobial Agents

- **Antiviral Agents**. Until recently, few effective antiviral agents were available for treating human infections. The reason for this is host toxicity. Viral replication requires the use of eukaryotic host cell enzymes, and the drugs that effectively interrupt viral replication are likely to interfere with host cell reproduction as well.
- However, in response to the AIDS epidemic, there has been massive, albeit delayed, development of antiretroviral agents.
- Almost all antiviral compounds are synthetic and, with few exceptions, the primary target of antiviral compounds is viral RNA or DNA synthesis. Agents such as acyclovir, ganciclovir, vidarabine, and ribavirin mimic the nucleoside building blocks of RNA and DNA.
- During active viral replication, the nucleoside analogs inhibit the viral DNA polymerase, preventing duplication of the viral genome and spread of infectious viral progeny to other susceptible host cells.

Antimicrobial Agents

- **Antifungal Agents**: The target site of the two most important families of antifungal agents is the cytoplasmic membranes of yeasts or molds.
- Fungal membranes differ from human cell membranes in that they contain the sterol ergosterol instead of cholesterol.
  - The polyene family of antifungal compounds (e.g., amphotericin B, nystatin) preferentially binds to ergosterol and forms holes in the cytoplasmic membrane, causing leakage of the fungal cell contents and, eventually, lysis of the cell.
  - The imidazole class of drugs (e.g., fluconazole, itraconazole, voriconazole, posaconazole) inhibits the synthesis of ergosterol, thereby damaging the integrity of the fungal cytoplasmic membrane.
  - A novel class of antifungal compounds called echinocandins has received considerable attention because these drugs inhibit the synthesis of β-1,3-glucan, a major cell wall polysaccharide found in many fungi, including C. albicans, Aspergillus species, and Pneumocystis carinii.

Antimicrobial Agents

- **Antiparasitic Agents**. Because of the extreme diversity of human parasites and their growth cycles, a review of antiparasitic therapies and agents would be highly impractical and lengthy.
- Similar to other infectious diseases caused by eukaryotic microorganisms, treatment of parasitic illnesses is based on exploiting essential components of the parasite's metabolism or cellular anatomy that are not shared by the host. Any relatedness between the target site of the parasite and the cells of the host increases the likelihood of toxic reactions in the host

Immunotherapy

- An exciting approach to the treatment of infectious diseases is immunotherapy. This strategy involves supplementing or stimulating the host's immune response so that the spread of a pathogen is limited or reversed. Several products are available for this purpose, including intravenous immunoglobulin (IVIG) and cytokines.
- IVIG is a pooled preparation of antibodies obtained from normal, healthy immune human donors that is infused as an intravenous solution. In theory, pathogen-specific antibodies present in the infusion facilitate neutralization, phagocytosis, and clearance of infectious agents above and beyond the capabilities of the diseased host.
- Hyperimmune immunoglobulin preparations, which are also commercially available, contain high titers of antibodies against specific pathogens, including hepatitis B virus, cytomegalovirus, rabies, and varicella–zoster virus.

Immunotherapy

- Cytokines are substances produced by various cells that, in small quantities, stimulate white cell replication, phagocytosis, antibody production, and the induction of fever, inflammation, and tissue repair—all of which counteract infectious agents and hasten recovery.
- Many cytokines, including interferons and interleukins, have been produced in the laboratory and are being evaluated experimentally as anti-infective agents.
- As we learn more about the action of cytokines, it becomes evident that some of the adverse reactions associated with infectious processes result from the body's own inflammatory response.
- Interventional therapies designed to inactivate certain cytokines such as tumor necrosis factor have proven to be helpful in animal models of infection.

Immunotherapy

- Immunization: Proper and timely adherence to recommended vaccination schedules in children and booster immunizations in adults effectively reduces the senseless spread of vaccine-preventable illnesses such as measles, mumps, pertussis, and rubella, which still occur with alarming frequency.

Surgical Intervention

- Today, medicinal therapy with antibiotics and other antiinfective agents is an effective solution for most infectious diseases. However, surgical intervention is still an important option for cases in which the pathogen is resistant to available treatments.
- Surgical interventions may be used to hasten the recovery process by providing access to an infected site by antimicrobial agents (drainage of an abscess), cleaning the site (debridement), or removing infected organs or tissue (e.g., appendectomy).

Good Luck!