Specialized English Two

School of Medicine

Shahid Beheshti University of Medical Sciences, Tehran-Iran

The present handout is prepared by Dr. Saeed Zarein, PhD in TEFL from Bristol University, England, Head of the English Language Department, School of Medicine. "I would like to thank my colleagues for their contributions in educating our doctors-to-be through this challenging handout."

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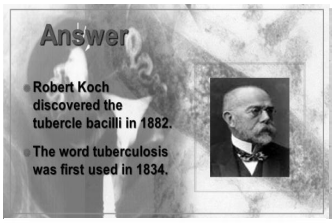
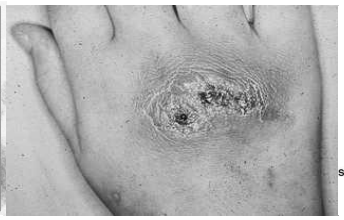
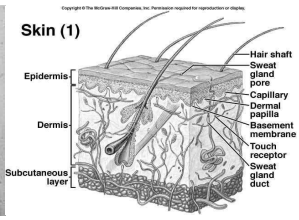
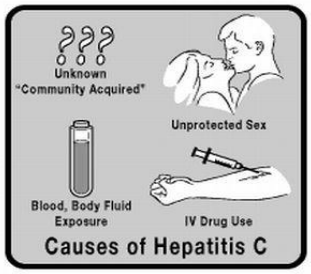
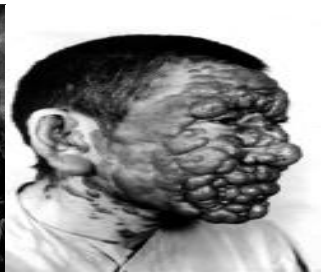










Unit 1: Infectious Diseases

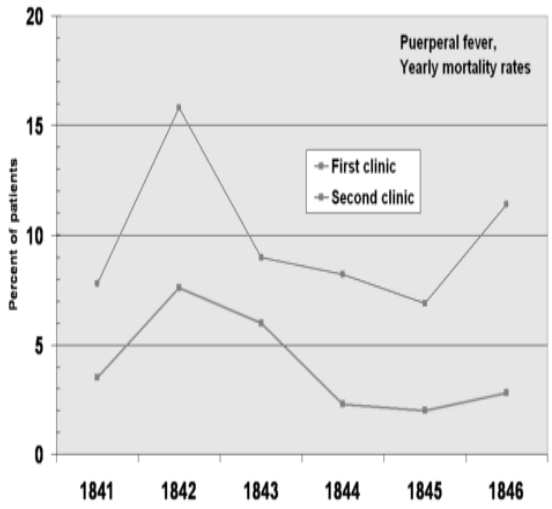
from Schartz's Principles of Surgery 17th Edition (2007)

Reading 1

Historical Background

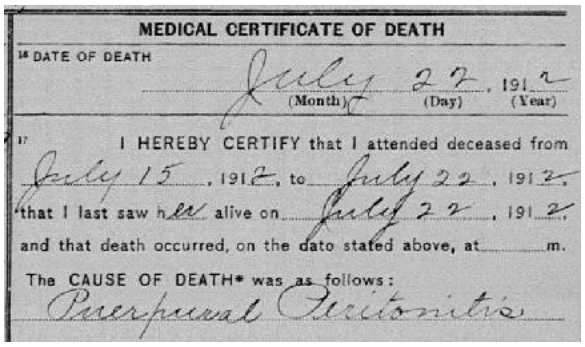
Although treatment of infection has been an integral part of the surgeon's practice since the dawn of time, the body of knowledge that led to the present field of surgical infectious disease was derived from the evolution of germ theory and antisepsis. Application of the latter to clinical practice, concurrent with the development of anesthesia, was pivotal in allowing surgeons to expand their repertoire to encompass complex procedures that previously were associated with extremely high rates of morbidity and mortality due to postoperative infections. However, until recently the occurrence of infection related to the surgical wound was the rule rather than the exception. In fact, the development of modalities to effectively prevent and treat infection has occurred only within the last several decades.

A number of observations by nineteenth-century physicians and investigators were critical to our current understanding of the pathogenesis, prevention, and treatment of surgical infections. In 1846, Ignaz Semmelweis, a Magyar physician, took a post at the Allgemein Krankenhaus in Vienna. He noticed that the mortality from puerperal ("childbed") fever was much higher in the teaching ward (1:11) than in the ward where patients were delivered by midwives (1:29). He also made the interesting observation that women who delivered prior to arrival on the teaching ward had a negligible mortality rate. The tragic death of a colleague due to overwhelming infection after a knife scratch received during an autopsy of a woman who had died of puerperal fever led Semmelweis to observe that pathologic changes in his friend were identical to those of women dying from this postpartum disease. He then hypothesized that puerperal fever was caused by putrid material transmitted from patients dying of this disease by carriage on the examining fingers of the medical students and physicians who frequently went from the autopsy room to the wards.



The low mortality noted in the midwives' ward, Semmelweis realized, was due to the fact that midwives did not participate in autopsies. Fired with the zeal of his revelation, he posted a notice on the door to the ward requiring all caregivers to rinse their hands thoroughly in chlorine water prior to entering

the area. This simple intervention reduced mortality from puerperal fever to 1.5%, surpassing the record of the midwives. In 1861, he published his classic work on childbed fever based on records from his practice.



MEDICAL CERTIFICATE OF DEATH

14 DATE OF DEATH July (Month) 22 (Day) 191[illegible] (Year)

17 I HEREBY CERTIFY that I attended deceased from July 15, 191[illegible], to July 22, 191[illegible],

that I last saw her alive on July 22, 191[illegible],

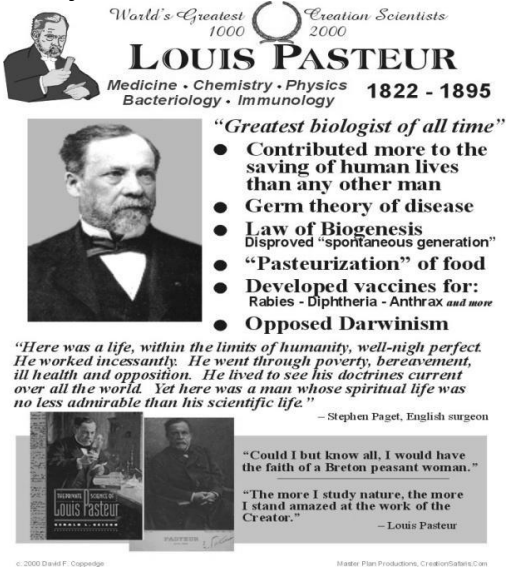
and that death occurred, on the date stated above, at ____ m.

The CAUSE OF DEATH* was as follows:

Puerperal Peritonitis

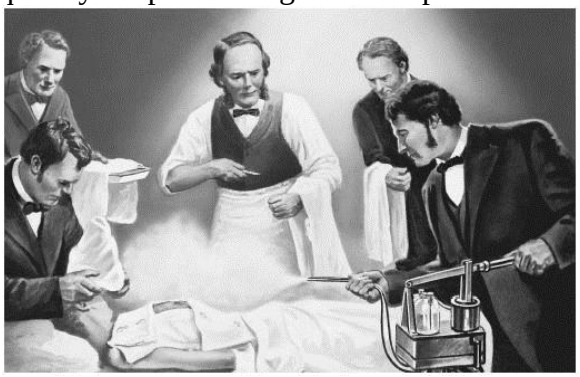
Unfortunately, Semmelweis' ideas were not well accepted by the authorities of the time. 1 Despondent, he committed suicide in 1865 by intentionally cutting his finger during the autopsy of a woman who died of puerperal fever, presumably as the ultimate proof of his tenets.

Louis Pasteur performed a body of work during the latter part of the nineteenth century that provided the underpinnings of modern microbiology, at the time known as "germ theory."



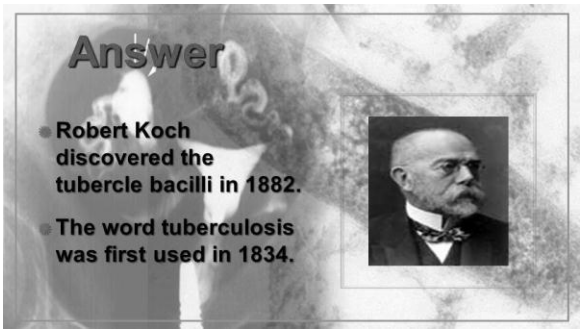
His work in humans followed experiments identifying infectious agents in silkworms. He was able to elucidate the principle that contagious diseases are caused by specific microbes and that these microbes are foreign to the infected organism. Using this principle he developed techniques of sterilization critical to oenology, and identified several bacteria responsible for human illnesses, including *Staphylococcus*,*Streptococcus*, and pneumococcus.

Joseph Lister, the son of a wine merchant, was appointed professor of surgery at the Glasgow Royal Infirmary in 1859. In his early practice, he noted that over 50% of his patients undergoing amputation died due to postoperative infection. After hearing of Pasteur's theory, Lister experimented with the use of a solution of carbolic acid, which he knew was being used to treat sewage. He first reported his findings to the British Medical Association in 1867 using dressings saturated with carbolic acid on 12 patients with compound fractures; 10 recovered without amputation, one survived with amputation, and one died of causes unrelated to the wound. In spite of initial resistance, his methods were quickly adopted throughout Europe.



From 1878 until 1880, Robert Koch was the District Medical Officer for Wollstein, which was an area in which anthrax was endemic. Performing experiments in his home, without the benefit of scientific equipment and academic contact, Koch developed techniques

for culture of *Bacillus anthracis* and proved the ability of this organism to cause anthrax in healthy animals. He developed the following four postulates to identify the association of organisms with specific diseases: (1) the suspected pathogenic organism should be present in all cases of the disease and absent from healthy animals, (2) the suspected pathogen should be isolated from a diseased host and grown in a pure culture in vitro, cells from a pure culture of the suspected organism should cause disease in a healthy animal, and the organism should be reisolated from the newly diseased animal and shown to be the same as the original. He used these same techniques to identify the organisms responsible for cholera and tuberculosis. During the next century, Koch's postulates, as they came to be called, became critical to our understanding of surgical infections and remain so today.



The first intra-abdominal operation to treat infection via "source control" (i.e., surgical intervention to eliminate the source of infection) was appendectomy. This operation was pioneered by Charles McBurney at the New York College of Physicians and Surgeons, among others. 3 McBurney's classic report on early operative intervention for appendicitis was presented before the New York Surgical Society in 1889. Appendectomy for the treatment of appendicitis, previously an often fatal disease, was popularized after the 1902 coronation of King Edward VII of England was delayed due to his need for an appendectomy, which was performed by Sir Frederick Treves. The king desperately needed an appendectomy but strongly opposed going into the hospital, protesting, "I have a coronation on hand." However, Treves was adamant, stating, "It will be a funeral, if you don't have the operation." Treves carried the debate, and the king lived.

During the twentieth century the discovery of effective antimicrobials added another tool to the armamentarium of modern surgeons. Sir Alexander Fleming, after serving in the British Army Medical Corps during World War I, continued work on the natural antibacterial action of the blood and antiseptics. In 1928, while studying influenza virus, he noted a zone of inhibition around a mold colony (*Penicillium notatum*) that serendipitously grew on a plate of *Staphylococcus,* and he named the active substance penicillin. This first effective antibacterial agent subsequently led to the development of hundreds of potent antimicrobials, set the stage for their use as prophylaxis against postoperative infection, and became a critical component of the armamentarium to treat aggressive, lethal surgical infections.

Reading 2

Concurrent with the development of numerous antimicrobial agents were advances in the field of clinical microbiology. Many new microbes were identified, including numerous anaerobes; the autochthonous microflora of the skin, gastrointestinal tract, and other parts of the body that the surgeon encountered in the process of an operation were characterized in great detail. However, it remained unclear

whether these organisms, anaerobes in particular, were commensals or pathogens. Subsequently, the initial clinical observations of surgeons such as Frank Meleney, William Altemeier, and others provided the key, when they observed that aerobes and anaerobes could synergize to cause serious soft tissue and severe intra-abdominal infection. 4,5 Thus, the concepts that resident microbes were nonpathogenic until they entered a sterile body cavity at the time of surgery, and that many, if not most, surgical infections were polymicrobial in nature, became critical ideas and were promulgated by a number of clinician-scientists over the last several decades. 6,7 These tenets became firmly established after microbiology laboratories demonstrated the invariable presence of aerobes and anaerobes in peritoneal cultures obtained at the time of surgery for intra-abdominal infection due to a perforated viscus or gangrenous appendicitis. Clinical trials provided evidence that optimal therapy for these infections required effective source control, plus the administration of antimicrobial agents directed against both types of pathogens.

William Osler, a prolific writer and one of the fathers of American medicine, made an observation in 1904 in his treatise *The Evolution of Modern Medicine* that was to have profound implications for the future of treatment of infection: "Except on few occasions, the patient appears to die from the body's response to infection rather than from it." 8 The discovery of the first cytokines began to allow insight into the organism's response to infection, and led to an explosion in our understanding of the host inflammatory response. Expanding knowledge of the multiple pathways activated during the response to invasion by infectious organisms has permitted the design of new therapies targeted at modifying the inflammatory response to infection, which seems to cause much of the end-organ dysfunction and failure. Preventing and treating this process of multiple organ failure during infection is one of the major challenges of modern critical care and surgical infectious disease.

Translation

Infection is the invasion of a host organism's body tissues by disease-causing agents, their multiplication, and the reaction of host tissues to these organisms and the toxins they produce. Infectious diseases, also known as transmissible diseases or communicable diseases, comprise clinically evident illness (i.e., characteristic medical signs and/or symptoms of disease) resulting from the infection, presence and growth of pathogenic biological agents in an individual host organism. Infections are caused by infectious agents such as viruses, iroids, and prions microorganisms such as bacteria, nematodes such as roundworms and pinworms, arthropods such as ticks, mites, fleas, and lice, fungi such as ringworm, and other macro-parasites such as tapeworms. Hosts can fight infections using their immune system. Mammalian hosts react to infections with an innate response, often involving inflammation, followed by an adaptive response. The branch of medicine that focuses on infections and pathogens is infectious disease medicine. Physicians and veterinarians may use specific pharmaceutical drugs to treat infections.
Bacterial infections are classified by the causative agent, as well as the symptoms and medical signs produced. Symptomatic infections are apparent, whereas an infection that is active but does not produce noticeable symptoms may be called inapparent, silent, or subclinical. An infection that is inactive or dormant is called a latent infection. A short-term infection is an acute infection. A long-term infection is a chronic infection.
Among the vast varieties of microorganisms, relatively few cause disease in otherwise healthy individuals.[4] Infectious disease results from the interplay between those few pathogens and the defenses of the hosts they infect. The appearance and severity of disease resulting from any pathogen, depends upon the ability of that pathogen to damage the host as well as the ability of the host to resist the pathogen. Clinicians therefore classify infectious microorganisms or microbes according to the status of host defenses - either as primary pathogens or as

Unit 2: Basic Considerations in Infectious Diseases

***from* Harrison's 18th Edition**

Reading 1

Introduction to Infectious Diseases: Host–Pathogen Interactions

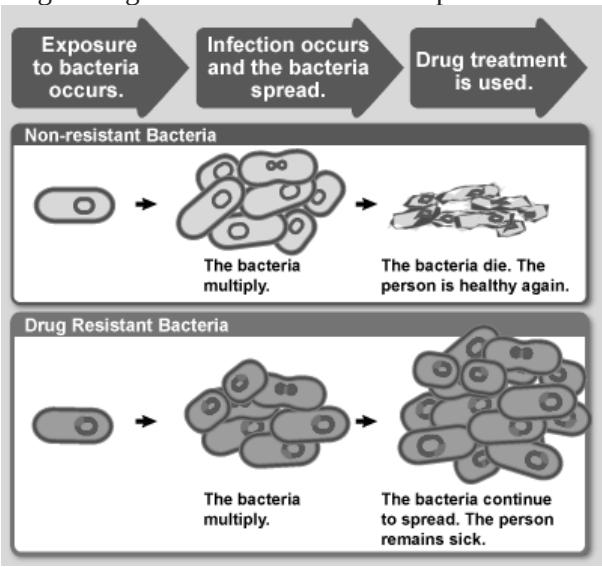
Lawrence C. Madoff, Dennis L. Kasper

Despite decades of dramatic progress in their treatment and prevention, infectious diseases remain a major cause of death and debility and are responsible for worsening the living conditions of many millions of people around the world. Infections frequently challenge the physician's diagnostic skill and must be considered in the differential diagnoses of syndromes affecting every organ system.

Changing epidemiology of infectious diseases

With the advent of antimicrobial agents, some medical leaders believed that infectious diseases would soon be eliminated and become of historic interest only. Indeed, the hundreds of chemotherapeutic agents developed since World War II, most of which are potent and safe, include drugs effective not only against bacteria but also against viruses, fungi, and parasites. Nevertheless, we now realize that as we developed antimicrobial agents, microbes developed the ability to elude our best weapons and to counterattack with new survival strategies.

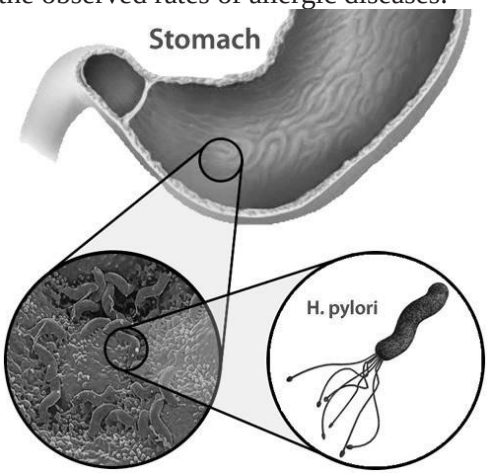
Antibiotic resistance occurs at an alarming rate among all classes of mammalian pathogens. Pneumococci resistant to penicillin and enterococci resistant to vancomycin have become commonplace. Even *Staphylococcus aureus* strains resistant to vancomycin have appeared. Such pathogens present real clinical problems in managing infections that were easily treatable just a few years ago. Diseases once thought to have been nearly eradicated from the developed world—tuberculosis, cholera, and rheumatic fever, for example—have rebounded with renewed ferocity. Newly discovered and emerging infectious agents appear to have been brought into contact with humans by changes in the environment and by movements of human and animal populations. An example of the propensity for pathogens to escape from their usual niche is the alarming 1999 outbreak in New York of encephalitis due to West Nile virus, which had never previously been isolated in the Americas. In 2003, severe acute respiratory syndrome (SARS) was first recognized. This emerging clinical entity is caused by a novel coronavirus that may have jumped from an animal niche to become a significant human pathogen. By 2006, H5N1 avian influenza, having spread rapidly through poultry farms in Asia and having caused deaths in exposed humans, had reached Europe and Africa, heightening fears of a new influenza pandemic.



Many infectious agents have been discovered only in recent decades. Ebola virus, human metapneumovirus, *Anaplasma phagocytophila* (the agent of human granulocytotropic ehrlichiosis), and retroviruses such as HIV humble us despite our deepening understanding of pathogenesis at the most basic molecular level. Even in developed countries, infectious diseases have made a resurgence. Between 1980 and 1996, mortality from infectious diseases in the United States increased by 64% to levels not seen since the 1940s.

The role of infectious agents in the etiology of diseases once believed to be noninfectious is increasingly recognized. For example, it is now widely accepted that *Helicobacter pylori* is the

causative agent of peptic ulcer disease and perhaps of gastric malignancy. Human papillomavirus is likely to be the most important cause of invasive cervical cancer. Human herpes virus type 8 is believed to be the cause of most cases of Kaposi's sarcoma. Epstein-Barr virus is a cause of certain lymphomas and may play a role in the genesis of Hodgkin's disease. The possibility certainly exists that other diseases of unknown cause, such as rheumatoid arthritis, sarcoidosis, or inflammatory bowel disease, have infectious etiologies. There is even evidence that atherosclerosis may have an infectious component. In contrast, there are data to suggest that decreased exposures to pathogens in childhood may be contributing to an increase in the observed rates of allergic diseases.



Medical advances against infectious diseases have been hindered by changes in patient populations. Immunocompromised hosts now constitute a significant proportion of the seriously infected population. Physicians immunosuppress their patients to prevent the rejection of transplants and to treat neoplastic and inflammatory diseases. Some infections, most notably that caused by HIV, immunocompromise the host in and of themselves. Lesser degrees of immunosuppression are associated with other infections, such as influenza and syphilis. Infectious agents that coexist peacefully with immunocompetent hosts wreak havoc in those who lack a complete immune system. AIDS has brought to prominence once-obscure organisms such as *Pneumocystis*, *Cryptosporidium parvum*, and *Mycobacterium avium*.

Reading 2

Host Factors in Infection

For any infectious process to occur, the pathogen and the host must first encounter each other. Factors such as geography, environment, and behavior thus influence the likelihood of infection. Although the initial encounter between a susceptible host and a virulent organism frequently results in disease, some organisms can be harbored in the host for years before disease becomes clinically evident. For a complete view, individual patients must be considered in the context of the population to which they belong. Infectious diseases do not often occur in isolation; rather, they spread through a group exposed from a point source (e.g., a contaminated water supply) or from one individual to another (e.g., via respiratory droplets). Thus, the clinician must be alert to infections prevalent in the community as a whole. A detailed history, including information on travel, behavioral factors, exposures to animals or potentially contaminated environments, and living and occupational conditions, must be elicited. For example, the likelihood of infection by *Plasmodium falciparum* can be significantly affected by altitude, climate, terrain, season, and even time of day. Antibiotic-resistant strains of *P. falciparum* are localized to specific geographic regions, and a seemingly minor alteration in a travel itinerary can dramatically influence the likelihood of acquiring chloroquine-resistant malaria. If such important details in the history are overlooked, inappropriate treatment may result in the death of the patient. Likewise, the chance of acquiring a sexually transmitted disease can be greatly affected by a relatively minor variation in sexual practices, such as the method used for contraception. Knowledge of the relationship between specific risk factors and disease allows the physician to influence a patient's health even before the development of infection by modification of these risk factors and—when a vaccine is available— by immunization.

Many specific host factors influence the likelihood of acquiring an infectious disease. Age, immunization history, prior illnesses, level of nutrition, pregnancy, coexisting illness, and perhaps emotional state all have some impact on

the risk of infection after exposure to a potential pathogen. The importance of individual host defense mechanisms, either specific or nonspecific, becomes apparent in their absence, and our understanding of these immune mechanisms is enhanced by studies of clinical syndromes developing in immunodeficient patients. For example, the higher attack rate of meningococcal disease among people with deficiencies in specific complement proteins of the so-called membrane attack complex (see "Adaptive Immunity," below) than in the general population underscores the importance of an intact complement system in the prevention of meningococcal infection.

Translation & Content Map

Infectious Diseases

The clinical manifestations of infectious diseases at presentation are myriad, varying from fulminant life-threatening processes to brief and self-limited conditions to indolent chronic maladies. A careful history is essential and must include details on underlying chronic diseases, medications, occupation, and travel. Risk factors for exposure to certain types of pathogens may give important clues to diagnosis. A sexual history may reveal risks for exposure to HIV and other sexually transmitted pathogens. A history of contact with animals may suggest numerous diagnoses, including rabies, Q fever, bartonellosis, Escherichia coli O157 infection, or cryptococcosis. Blood transfusions have been linked to diseases ranging from viral hepatitis to malaria to prion disease. A history of exposure to insect vectors (coupled with information about the season and geographic site of exposure) may lead to consideration of such diseases as Rocky Mountain spotted fever, other rickettsial diseases, tularemia, Lyme disease, babesiosis, malaria, trypanosomiasis, and numerous arboviral infections. Ingestion of contaminated liquids or foods may lead to enteric infection with Salmonella, Listeria, Campylobacter, amebas, cryptosporidia, or helminths. Since infectious diseases may involve many organ systems, a careful review of systems may elicit important clues as to the disease process.

The physical examination must be thorough, and attention must be paid to seemingly minor details, such as a soft heart murmur that might indicate bacterial endocarditis or a retinal lesion that suggests disseminated candidiasis or cytomegalovirus (CMV) infection. Rashes are extremely important clues to infectious diagnoses and may be the only sign pointing to a specific etiology (Chap. 18; Chap. e5). Certain rashes are so specific as to be pathognomonic— e.g., the childhood exanthems (measles, rubella, varicella), the target lesion of erythema migrans (Lyme disease), ecthyma gangrenosum (Pseudomonas aeruginosa), and eschars (rickettsial diseases). Other rashes, although less specific, may be exceedingly important diagnostic indicators. The prompt recognition of the early scarlatiniform and later petechial rashes of meningococcal infection or of the subtle embolic lesions of disseminated fungal infections in immunosuppressed patients can hasten lifesaving therapy. Fever (Chaps. 17, 18, and 19) is a common manifestation of infection and may be its sole apparent indication. Sometimes the pattern of fever or its temporally associated findings may help refine the differential diagnosis. For example, fever occurring every 48–72 h is suggestive of malaria (Chap. 203). The elevation in body temperature in fever (through resetting of the hypothalamic setpoint mediated by cytokines) must be distinguished from elevations in body temperature from other causes such as drug toxicity (Chap. 19) or heat stroke (Chap. 17).

Unit 3: Molecular Mechanisms of Microbial Pathogenesis and Tissue Damage

Reading 1

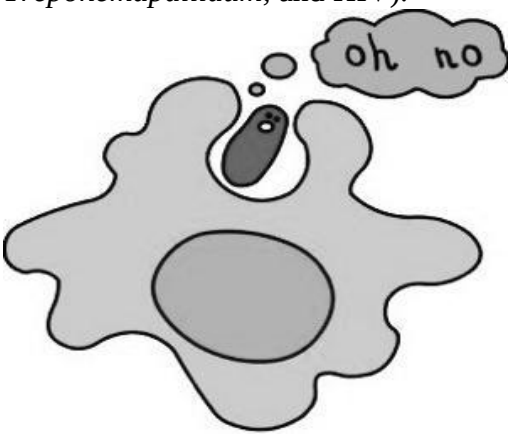
Over the past four decades, molecular studies of the pathogenesis of microorganisms have yielded an explosion of information about the various microbial and host molecules that contribute to the processes of infection and disease. These processes can be classified into several stages: microbial encounter with and entry into the host; microbial growth after entry; avoidance of innate host defenses; tissue invasion and tropism; tissue damage; and transmission to new hosts. *Virulence* is the measure of an organism's capacity to cause disease and is a function of the pathogenic factors elaborated by microbes. These factors promote *colonization* (the simple presence of potentially pathogenic microbes in or on a host), *infection* (attachment and growth of pathogens and avoidance of host defenses), and *disease* (often, but not always, the result of activities of secreted toxins or toxic metabolites). In addition, the host's inflammatory response to infection greatly contributes to disease and its attendant clinical signs and symptoms.

Microbial Entry and Adherence

Entry Sites

A microbial pathogen can potentially enter any part of a host organism. In general, the type of disease produced by a particular microbe is often a direct consequence of its route of entry into the body. The most common sites of entry are mucosal surfaces (the respiratory, alimentary, and urogenital tracts) and the skin. Ingestion, inhalation, and sexual contact are typical routes of microbial entry. Other portals of entry include sites of skin injury (cuts, bites, burns, trauma) along with injection via natural (i.e., vector-borne) or artificial (i.e., needle-stick injury) routes. A few pathogens, such as *Schistosoma* species, can penetrate unbroken skin. The conjunctiva can serve as an entry point for pathogens of the eye, which occasionally spread systemically from that site.

Microbial entry usually relies on the presence of specific factors needed for persistence and growth in a tissue. Fecal-oral spread via the alimentary tract requires a biologic profile consistent with survival in the varied environments of the gastrointestinal tract (including the low pH of the stomach and the high bile content of the intestine) as well as in contaminated food or water outside the host. Organisms that gain entry via the respiratory tract survive well in small moist droplets produced during sneezing and coughing. Pathogens that enter by venereal routes often survive best in the warm moist environment of the urogenital mucosa and have restricted host ranges (e.g., *Neisseria gonorrhoeae*, *Treponemapallidum*, and HIV).



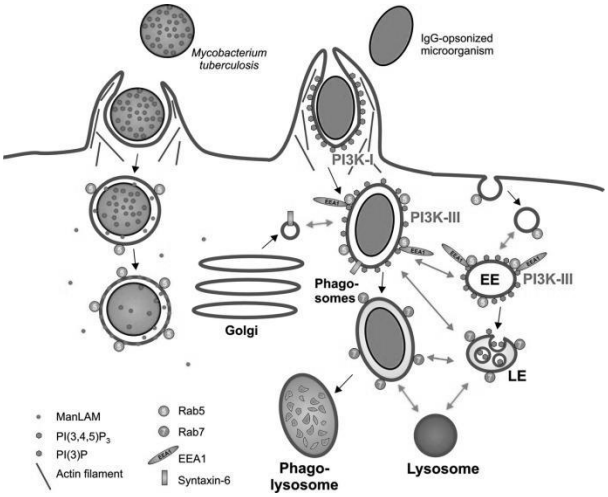
Phagocytosis and Inflammation

Phagocytosis of microbes is a major innate host defense that limits the growth and spread of pathogens. Phagocytes appear rapidly at sites of infection in conjunction with the initiation of inflammation. Ingestion of microbes by both tissue-fixed macrophages

and migrating phagocytes probably accounts for the limited ability of most microbial agents to cause disease. A family of related molecules called *collectins*, *soluble defense collagens*, or *pattern-recognition molecules* are found in blood (mannose-binding lectins), in lung (surfactant proteins A and D), and most likely in other tissues as well and bind to carbohydrates on microbial surfaces to promote phagocyte clearance. Bacterial pathogens seem to be ingested principally by polymorphonuclear neutrophils, while eosinophils are frequently found at sites of infection by protozoan or multicellular parasites. Successful pathogens, by definition, must avoid being cleared by professional phagocytes. One of several antiphagocytic strategies employed by bacteria and by the fungal pathogen *Cryptococcus neoformans* is to elaborate large-molecular-weight surface polysaccharide antigens, often in the form of a capsule that coats the cell surface. Most pathogenic bacteria produce such antiphagocytic capsules. On occasion, proteins or polypeptides form capsule-like coatings for organisms such as group A streptococci and *Bacillus anthracis*.

Additional Interactions of Microbial Pathogens and Phagocytes

Other ways that microbial pathogens avoid destruction by phagocytes include production of factors that are toxic to the phagocytes or that interfere with the chemotactic and ingestion function of phagocytes. Hemolysins, leukocidins, and the like are microbial proteins that can kill phagocytes that are attempting to ingest organisms elaborating these substances. For example, staphylococcal hemolysins inhibit macrophage chemotaxis and kill these phagocytes. Streptolysin O made by *S. pyogenes* binds to cholesterol in phagocyte membranes and initiates a process of internal degranulation, with the release of normally granule-sequestered toxic components into the phagocyte's cytoplasm. *E. histolytica*, an intestinal protozoan that causes amebic dysentery, can disrupt phagocyte membranes after direct contact via the release of protozoal phospholipase A and pore-forming peptides.



Microbial Survival inside Phagocytes

Many important microbial pathogens use a variety of strategies to survive inside phagocytes (particularly macrophages) after ingestion. Inhibition of fusion of the phagocytic vacuole (the phagosome) containing the ingested microbe with the lysosomal granules containing antimicrobial substances (the lysosome) allows *Mycobacterium tuberculosis*, *S. enterica* serovar Typhi, and *Toxoplasma gondii* to survive inside macrophages. Some organisms, such as *Listeria monocytogenes*, escape into the phagocyte's cytoplasm to grow and eventually spread to other cells. Resistance to killing within the macrophage and subsequent growth are critical to successful infection by herpes-type viruses, measles virus, poxviruses, *Salmonella*, *Yersinia*, *Legionella*, *Mycobacterium*, *Trypanosoma*, *Nocardia*, *Histoplasma*, *Toxoplasma*, and *Rickettsia*. *Salmonella* species use a master regulatory system—in which the *PhoP*/*PhoQ* genes control other genes—to enter and survive within cells, with intracellular survival

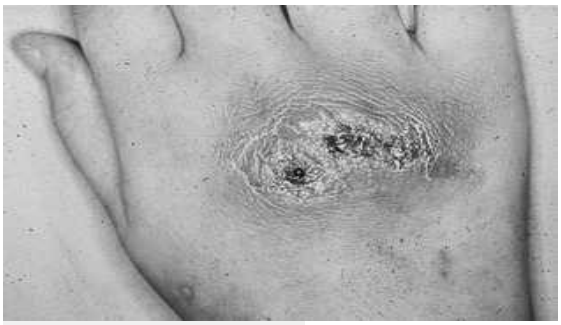
entailing structural changes in the cell envelope LPS.

Reading 2

Tissue Invasion and Tissue Tropism

Most viral pathogens cause disease by growth at skin or mucosal entry sites, but some pathogens spread from the initial site to deeper tissues. Virus can spread via the nerves (rabies virus) or plasma (picornaviruses) or within migratory blood cells (poliovirus, Epstein-Barr virus, and many others). Specific viral genes determine where and how individual viral strains can spread.

Bacteria may invade deeper layers of mucosal tissue via intracellular uptake by epithelial cells, traversal of epithelial cell junctions, or penetration through denuded epithelial surfaces. Among virulent *Shigella* strains and invasive *E. coli*, outer-membrane proteins are critical to epithelial cell invasion and bacterial multiplication. *Neisseria* and *Haemophilus* species penetrate mucosal cells by poorly understood mechanisms before dissemination into the bloodstream. Staphylococci and streptococci elaborate a variety of extracellular enzymes, such as hyaluronidase, lipases, nucleases, and hemolysins, that are probably important in breaking down cellular and matrix structures and allowing the bacteria access to deeper tissues and blood. Organisms that colonize the gastrointestinal tract can often translocate through the mucosa into the blood and, under circumstances in which host defenses are inadequate, cause bacteremia. *Y. enterocolitica* can invade the mucosa through the activity of the invasin protein. Some bacteria (e.g., *Brucella*) can be carried from a mucosal site to a distant site by phagocytic cells (e.g., polymorphonuclear neutrophils) that ingest but fail to kill the bacteria.



Aspergillus fumigatus- Disease

Fungal pathogens almost always take advantage of host immunocompromise to spread hematogenously to deeper tissues. The AIDSepidemic has resoundingly illustrated this principle: the immunodeficiency of many HIV-infected patients permits the development of life-threatening fungal infections of the lung, blood, and brain. Other than the capsule of *C. neoformans*, specific fungal antigens involved in tissue invasion are not well characterized. Both fungal pathogens and protozoal pathogens (e.g., *Plasmodium* species and *E. histolytica*) undergo morphologic changes to spread within a host. Malarial parasites grow in liver cells as merozoites and are released into the blood to invade erythrocytes and become trophozoites. *E. histolytica* is found as both a cyst and a trophozoite in the intestinal lumen, through which this pathogen enters the host, but only the trophozoite form can spread systemically to cause amebic liver abscesses. Other protozoal pathogens, such as *T. gondii*, *Giardia lamblia*, and *Cryptosporidium*, also undergo extensive morphologic changes after initial infection to spread to other tissues.

Unit 4: Approach to the Acutely Ill Infected Febrile Patient and Patient Experiencing Pain

Reading 1

Introduction

The physician treating the acutely ill febrile patient must be able to recognize infections that require emergent attention. If such infections are not adequately evaluated and treated at initial presentation, the opportunity to alter an adverse outcome may be lost. In this chapter, the clinical presentations of and approach to patients with relatively common infectious disease emergencies are discussed. These infectious processes and their treatments are discussed in detail in other chapters.

Before the history is elicited and a physical examination performed, an immediate assessment of the patient's general appearance can yield valuable information. The perceptive physician's subjective sense that a patient is septic or toxic often proves accurate. Visible agitation or anxiety in a febrile patient can be a harbinger of critical illness.

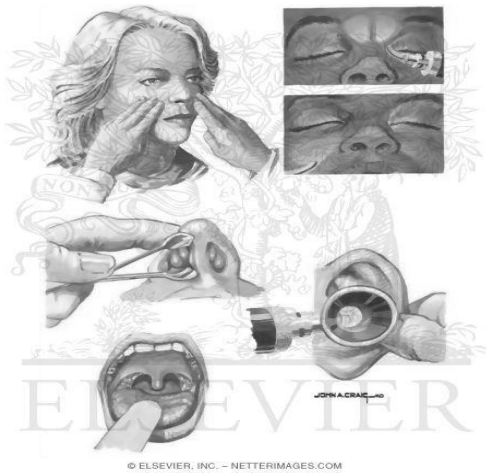
History

Presenting symptoms are frequently nonspecific. Detailed questions should be asked about the onset and duration of symptoms and about changes in severity or rate of progression over time. Host factors and comorbid conditions may enhance the risk of infection with certain organisms or of a more fulminant course than is usually seen. Lack of splenic function, alcoholism with significant liver disease, IV drug use, HIV infection, diabetes, malignancy, organ transplantation, and chemotherapy all predispose to specific infections and frequently to increased severity. The patient should be questioned about factors that might help identify a nidus for invasive infection, such as recent upper respiratory tract infections, influenza, or varicella; prior trauma; disruption of cutaneous barriers due to lacerations, burns, surgery, body piercing, or decubiti; and the presence of foreign bodies, such as nasal packing after rhinoplasty, tampons, or prosthetic joints. Travel, contact with pets or other animals, or activities that might result in tick or mosquito exposure can lead to diagnoses that would not otherwise be considered. Recent dietary intake, medication use, social or occupational contact with ill individuals, vaccination history, recent sexual contacts, and menstrual history may be relevant. A review of systems should focus on any neurologic signs or sensorium alterations, rashes or skin lesions, and focal pain or tenderness and should also include a general review of respiratory, gastrointestinal, or genitourinary symptoms.

Physical Examination

A complete physical examination should be performed, with special attention to several areas that are sometimes given short shrift in routine examinations. Assessment of the patient's general appearance and vital signs, skin and soft tissue examination, and the

neurologic evaluation are of particular importance.



The patient may appear either anxious and agitated or lethargic and apathetic. Fever is usually present, although elderly patients and compromised hosts [e.g., patients who are uremic or cirrhotic and those who are taking glucocorticoids or nonsteroidal anti-inflammatory drugs (NSAIDs)] may be afebrile despite serious underlying infection. Measurement of blood pressure, heart rate, and respiratory rate helps determine the degree of hemodynamic and metabolic compromise. The patient's airway must be evaluated to rule out the risk of obstruction from an invasive oropharyngeal infection.

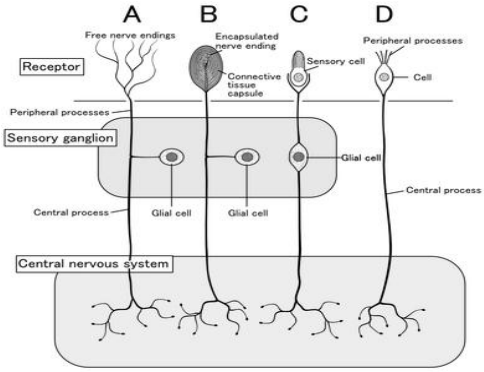
The etiologic diagnosis may become evident in the context of a thorough skin examination (Chap. 17). Petechial rashes are typically seen with meningococcemia or Rocky Mountain spotted fever (RMSF; see Fig. e7-16); erythroderma is associated with toxic shock syndrome (TSS) and drug fever. The soft tissue and muscle examination is critical. Areas of erythema or duskiness, edema, and tenderness may indicate underlying necrotizing fasciitis, myositis, or myonecrosis. The neurologic examination must include a careful assessment of mental status for signs of early encephalopathy. Evidence of nuchal rigidity or focal neurologic findings should be sought.

Immunization Principles and Vaccine Use: Introduction

Few medical interventions of the past century can rival the effect that immunization has had on longevity, economic savings, and quality of life. Seventeen diseases are now preventable through vaccines routinely administered to children and adults in the United States, and most vaccine-preventable diseases of childhood are at historically low levels. Health care providers deliver the vast majority of vaccines in the United States in the course of providing routine health services and therefore play an integral role in the nation's public health system.

The Pain Sensory System

Pain is an unpleasant sensation localized to a part of the body. It is often described in terms of a penetrating or tissue-destructive process (e.g., stabbing, burning, twisting, tearing, squeezing) and/or of a bodily or emotional reaction (e.g., terrifying, nauseating, sickening). Furthermore, any pain of moderate or higher intensity is accompanied by anxiety and the urge to escape or terminate the feeling.

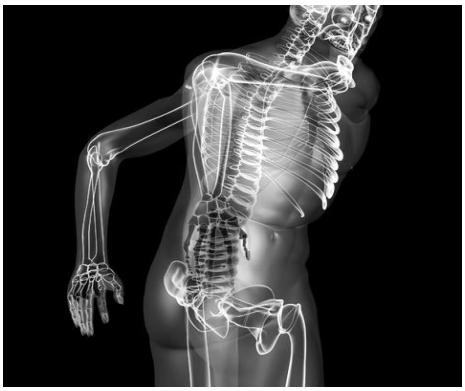


These properties illustrate the duality of pain: it is both sensation and emotion. When it is acute, pain is characteristically associated with behavioral arousal and a stress response consisting of increased blood pressure, heart

rate, pupil diameter, and plasma cortisol levels. In addition, local muscle contraction (e.g., limb flexion, abdominal wall rigidity) is often present.

Treatment: Acute Pain

The ideal treatment for any pain is to remove the cause; thus, while treatment can be initiated immediately, efforts to establish the underlying etiology should always proceed as treatment begins. Sometimes, treating the underlying condition does not immediately relieve pain. Furthermore, some conditions are so painful that rapid and effective analgesia is essential (e.g., the postoperative state, burns, trauma, cancer, or sickle cell crisis). Analgesic medications are a first line of treatment in these cases, and all practitioners should be familiar with their use.



Aspirin, Acetaminophen, and Nonsteroidal Anti-Inflammatory Agents (NSAIDs)

These drugs are considered together because they are used for similar problems and may have a similar mechanism of action All these compounds inhibit cyclooxygenase (COX), and, except for acetaminophen, all have anti-inflammatory actions, especially at higher dosages. They are particularly effective for mild to moderate headache and for pain of musculoskeletal origin.

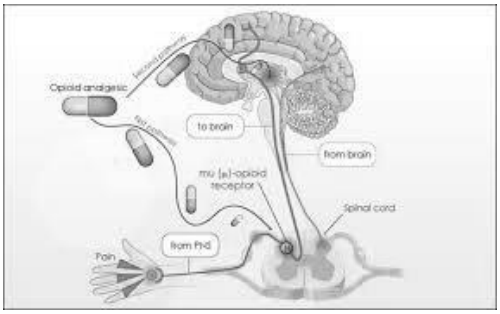
Because they are effective for these common types of pain and are available without prescription, COX inhibitors are by far the most commonly used analgesics. They are absorbed well from the gastrointestinal tract and, with occasional use, have only minimal side effects. With chronic use, gastric irritation is a common side effect of aspirin and NSAIDs and is the problem that most frequently limits the dose that can be given. Gastric irritation is most severe with aspirin, which may cause erosion and ulceration of the gastric mucosa leading to bleeding or perforation. Because aspirin irreversibly acetylates platelet cyclooxygenase and thereby interferes with coagulation of the blood, gastrointestinal bleeding is a particular risk. Older age and history of gastrointestinal disease increase the risks of aspirin and NSAIDs. In addition to the well-known gastrointestinal toxicity of NSAIDs, nephrotoxicity is a significant problem for patients using these drugs on a chronic basis. Patients at risk for renal insufficiency, particularly those with significant contraction of their intravascular volume as occurs with chronic diuretic use or acute hypovolemia, should be monitored closely. NSAIDs can also increase blood pressure in some individuals. Long-term treatment with NSAIDs requires regular blood pressure monitoring and treatment if necessary. Although toxic to the liver when taken in high doses, acetaminophen rarely produces gastric irritation and does not interfere with platelet function.

The introduction of a parenteral form of NSAID, ketorolac, extends the usefulness of this class of compounds in the management of acute severe pain. Ketorolac is sufficiently potent and rapid in onset to supplant opioids for many patients with acute severe headache and musculoskeletal pain.

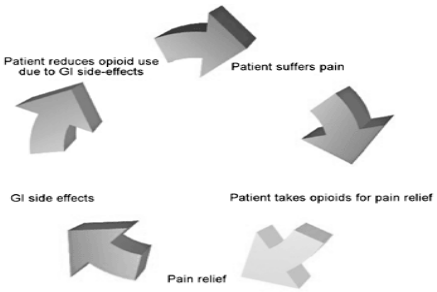
Reading 2

Opioid Analgesics

Opioids are the most potent pain-relieving drugs currently available. Of all analgesics, they have the broadest range of efficacy and provide the most reliable and effective method for rapid pain relief. Although side effects are common, most are reversible: nausea, vomiting, pruritus, and constipation are the most frequent and bothersome side effects. Respiratory depression is uncommon at standard analgesic doses, but can be life-threatening. Opioid-related side effects can be reversed rapidly with the narcotic antagonist naloxone. The physician should not hesitate to use opioid analgesics in patients with acute severe pain.



Opioids produce analgesia by actions in the CNS. They activate pain-inhibitory neurons and directly inhibit pain-transmission neurons. Most of the commercially available opioid analgesics act at the same opioid receptor (-receptor), differing mainly in potency, speed of onset, duration of action, and optimal route of administration. Some side effects are due to accumulation of nonopioid metabolites that are unique to individual drugs. One striking example of this is normeperidine, a metabolite of meperidine. Normeperidine produces hyperexcitability and seizures that are not reversible with naloxone. Normeperidine accumulation is increased in patients with renal failure.



The most rapid relief with opioids is obtained by intravenous administration; relief with oral administration is significantly slower. Common side effects include nausea, vomiting, constipation, and sedation. The most serious side effect is respiratory depression. Patients with any form of respiratory compromise must be kept under close observation following opioid administration; an oxygen-saturation monitor may be useful. Opioid-induced respiratory depression is typically accompanied by significant sedation and a reduction in respiratory rate. A fall in oxygen saturation represents a critical level of respiratory depression and the need for immediate intervention to prevent life-threatening hypoxemia. Ventilatory assistance should be maintained until the opioid-induced respiratory depression has resolved. The opioid antagonist naloxone should be readily available whenever opioids are used at high doses or in patients with compromised pulmonary function. Opioid effects are dose-related, and there is great variability among patients in the doses that relieve pain and produce side effects. Because of this, initiation of therapy requires titration to optimal dose and interval. The most important principle is to provide adequate pain relief. This requires determining whether the drug has adequately relieved the pain and frequent reassessment to determine the optimal interval for dosing. *The most common error made by physicians in managing severe pain with opioids is to prescribe an inadequate dose. Because many patients are reluctant to complain, this practice leads to needless suffering*. In the

absence of sedation at the expected time of peak effect, a physician should not hesitate to repeat the initial dose to achieve satisfactory pain relief.

An innovative approach to the problem of achieving adequate pain relief is the use of patient-controlled analgesia (PCA). PCA uses a microprocessor-controlled infusion device that can deliver a baseline continuous dose of an opioid drug as well as preprogrammed additional doses whenever the patient pushes a button. The patient can then titrate the dose to the optimal level. This approach is used most extensively for the management of postoperative pain, but there is no reason why it should not be used for any hospitalized patient with persistent severe pain. PCA is also used for short-term home care of patients with intractable pain, such as that caused by metastatic cancer.

It is important to understand that the PCA device delivers small, repeated doses to maintain pain relief; in patients with severe pain, the pain must first be brought under control with a loading dose before transitioning to the PCA device. The bolus dose of the drug (typically 1 mg morphine, 0.2 mg of hydromorphone, or 10 g fentanyl) can then be delivered repeatedly as needed. To prevent overdosing, PCA devices are programmed with a lockout period after each demand dose is delivered (5–10 min) and a limit on the total dose delivered per hour. While some have advocated the use of a simultaneous continuous or basal infusion of the PCA drug, this increases the risk of respiratory depression and has not been shown to increase the overall efficacy of the technique.

Translation

Many physicians, nurses, and patients have a certain trepidation about using opioids that is based on an exaggerated fear of addiction. In fact, there is a vanishingly small chance of patients becoming addicted to narcotics as a result of their appropriate medical use.

The availability of new routes of administration has extended the usefulness of opioid analgesics. Most important is the availability of spinal administration. Opioids can be infused through a spinal catheter placed either intrathecally or epidurally. By applying opioids directly to the spinal or epidural space adjacent to the spinal cord, regional analgesia can be obtained using relatively low total doses. Indeed, the dose required to produce effective localized analgesia when using morphine intrathecally (0.1–0.3 mg) is a fraction of that required to produce similar analgesia when administered intravenously (5–10 mg). In this way, side effects such as sedation, nausea, and respiratory depression can be minimized. This approach has been used extensively in obstetric procedures and for postoperative pain relief following surgical procedures on the lower extremities. Continuous intrathecal delivery via implanted spinal drug-delivery systems is now commonly used, particularly for the treatment of cancer-related pain that would require sedating doses for adequate pain control if given systemically. Opioids can also be given intranasally (butorphanol), rectally, and transdermally (fentanyl), thus avoiding the discomfort of frequent injections in patients who cannot be given oral medication. The fentanyl transdermal patch has the advantage of providing fairly steady plasma levels, which maximizes patient comfort.

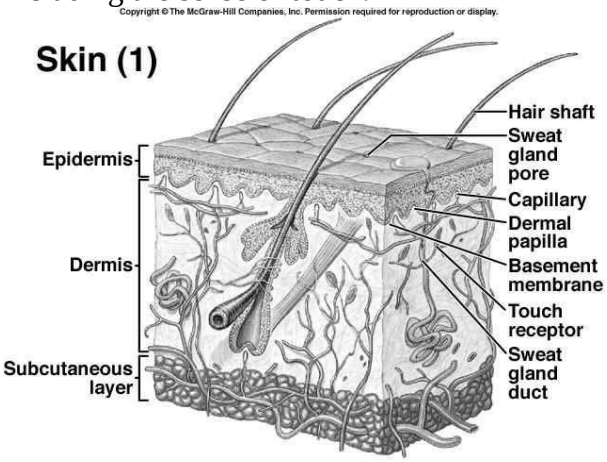
Recent additions to the armamentarium for treating opioid-induced side effects are the peripherally acting opioid antagonists alvimopan (Entereg) and methylnaltrexone (Rellistor). Alvimopan is available as an orally administered agent that is restricted to the intestinal lumen by limited absorption; methylnaltrexone is available in a subcutaneously administered form that has virtually no penetration into the CNS. Both agents act by binding to peripheral -receptors, thereby inhibiting or reversing the effects of opioids at these peripheral sites. The action of both agents is restricted to receptor sites outside of the CNS; thus, these drugs can reverse the adverse effects of opioid analgesics that are mediated through their peripheral receptors without reversing their analgesic effects. Both agents are effective for persistent ileus following abdominal surgery to the extent that opioid analgesics used for postoperative pain control contribute to this serious problem. Likewise, both agents have been tested for their effectiveness in treating opioid-induced bowel dysfunction (constipation) in patients taking opioid analgesics on a chronic basis.

Unit 5: Integumentary system

Reading 1

Anatomy and Physiology

The skin, also called *integument*, is the largest organ in the body. Together with its accessory organs (hair, nails, and glands), the skin makes up the **integumentary system.** Its elaborate system of distinct tissues includes glands that produce several types of secretions, nerves that transmit impulses, and blood vessels that help regulate body temperature. The skin covers and protects all outer surfaces of the body and performs many vital functions, including the sense of touch.



Skin

The skin protects underlying structures from injury and provides sensory information to the brain. Beneath the skin's surface is an intricate network of nerve fibers that register sensations of temperature, pain, and pressure. Other important functions of the skin include protecting the body against ultraviolet rays, regulating body temperature, and preventing dehydration. The skin also acts as a reservoir for food and water. It also synthesizes vitamin D when exposed to sunlight. The skin consists of two distinct layers: the epidermis and the dermis. A subcutaneous layer of tissue binds the skin to underlying structures.

Epidermis

The outer layer, the (1) **epidermis,** is relatively thin over most areas but is thickest on the palms of the hands and the soles of the feet. Although the epidermis is composed of several sublayers called ***strata***, the (2) **stratum corneum** and the (3) **basal layer**, which is the deepest layer, are of greatest importance. The stratum corneum is composed of dead flat cells that lack a blood supply and sensory receptors. Its thickness is correlated with normal wear of the area it covers. The basal layer is the only layer of the epidermis that is composed of living cells,

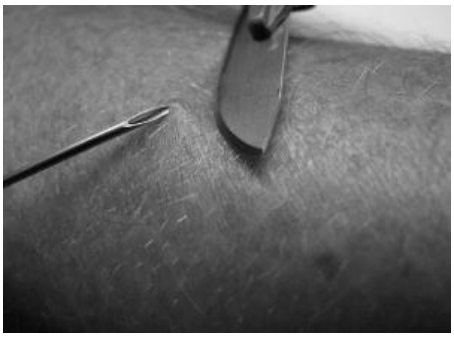
Skin and Subcutaneous Tissue

*f*rom Schartz's Principles of Surgery (17th Edition) (2007)

The skin is the largest and among the most complex organs of the body. Its uniform appearance belies its great variation from region to region of the body and the complex organization and interaction of the many different cells and matrices of the skin. Although the skin functions simply as a protective barrier to interface with our environment, its structure and physiology are complex.

In its role as an environmental buffer, the skin protects against most noxious agents, such as chemicals (by the impermeability of the epidermis), solar radiation (by means of pigmentation), infectious agents (through efficient immunosurveillance), and physically deforming forces (by the durability of the dermis). Its efficient ability to conserve or disperse heat makes the skin the major organ responsible for thermoregulation. To direct all these functions, the skin has a highly specialized nervous structure.

These various functions are better served by different components of skin, so that teleologically regional variation develops. The palms and soles are particularly thick, to bear weight. The fingertips have the highest density of sensory innervation and allow for intricate tasks. Even the lines of the skin, first described by Langer, are oriented perpendicularly to the long axis of muscles to allow the greatest degree of stretching and contraction without deformity.



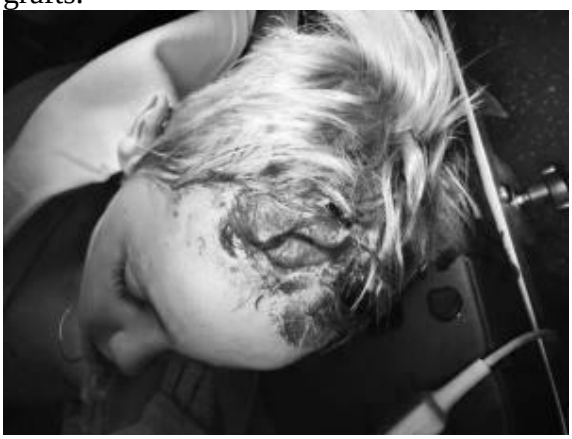
The relative ease of observing and obtaining skin specimens for examination and experiments has made the skin one of the best-studied tissues of the human body. Thus, the study of skin is not just the subject of the field of dermatology, but also has launched the fields of immunology, transplantation, and wound healing. 2,3 Although this chapter emphasizes surgically treated diseases of the skin, it is important for students of surgery to be familiar with the basic physiology and structure of skin because many of the future advances in medicine will come from these studies.

Injuries to Skin and Subcutaneous Tissue

Injuries that violate the continuity of the skin and subcutaneous tissue can occur as a result of trauma or from various environmental exposures. Environmental exposures that damage the skin and subcutaneous tissues include caustic substances, exposure to extreme temperatures, prolonged or excessive pressure, and exposure to radiation. Disruption of the continuity of the skin allows the entry of organisms that can lead to local or systemic infection.

Traumatic Injuries

Traumatic wounds include penetrating, blunt, and shear forces (sliding against a fixed surface), bite, and degloving injuries. Sharp lacerations, bullet wounds, "road rash" (injury from scraping against road pavement), and degloving injuries should be treated by gentle cleansing, débridement of all foreign debris and necrotic tissue, and application of a proper dressing. Dirty or infected wounds should be left open to heal by secondary intention or delayed primary closure. Clean lacerations may be closed primarily. Road rash injuries are treated as second-degree burns and degloving injuries as third-degree or full-thickness burns. The degloved skin can be placed back on the wound like a skin graft and assessed daily for survival. If the skin becomes necrotic, it is débrided and the wound is covered with split-thickness skin grafts.



Special consideration should be given to bite wounds. It is estimated that 4.5 million bites occur annually, accounting for 2% of all visits to emergency rooms. 19 Common bite wounds include those delivered by either a human or canine. The most serious human bite is that of a clenched fist injury. This occurs when the

closed fist hits a person's teeth, often during a fight, termed "fight bite." These small wounds may seem innocuous but can lead to significant morbidity if not recognized early and treated, given that the human oral flora contains multiple species of aerobic and anaerobic bacteria. The most common infectious organisms found with human bites are *Viridans streptococci*, *Staphylococcus aureus*, *Eikenella corrodens*, *Haemophilus influenzae*, and beta-lactamase-producing bacteria. 20 The underlying metacarpophalangeal joint is susceptible to injury because it can be penetrated and inoculated with organisms, as can the underlying bone or tendon. The management of these wounds includes drainage, copious irrigation, antibiotic therapy, extremity immobilization, and elevation. Dog bites account for the most common animal bite wound. Dog bites differ from human bites in that they are a more crushing-type injury because of the animal's round teeth and strong jaws. The dog's jaw can exert more than 450 pounds of pressure per square inch. 21 This pressure has a greater potential to disrupt structures deep to the skin and subcutaneous tissues such as bones, vessels, tendons, muscles, and nerves. Mixed organisms, both aerobic and anaerobic, have been cultured from dog bite wounds. The most common organisms include *Pasteurella multocida*, *Staphylococcus* species, alpha-hemolytic streptococci, *Eikenella corrodens*, *Actinomyces*, and *Fusobacterium*. 20 The management of these wounds includes copious irrigation, débridement of devitalized tissue, and antibiotic therapy.

Reading 2

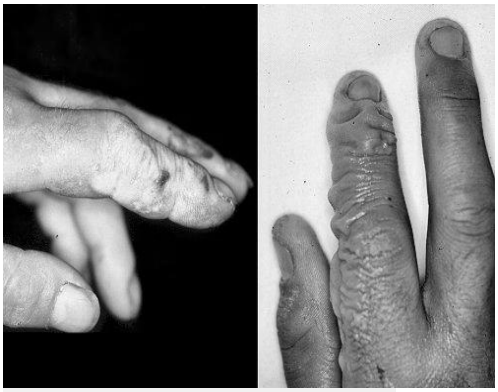
Exposure to Caustic Substances

Many substances can disrupt the integrity of the skin. Injuries commonly seen by physicians are those caused by environmental chemicals, either alkali or acidic solutions, or may occur iatrogenically as a complication of intravenous fluid administration.
Alkaline agents, which are often used as industrial-grade cleaning solvents and household cleaning agents, are responsible for more than 15,000 skin burns in the United States annually.

Acute alkali burn of great severity. Marked involvement of facial skin is apparent

After penetrating the skin, alkaline substances cause saponification of fat, which allows for deeper penetration and increased tissue damage. Management of these injuries should be rapid as the tissue damage produced by alkaline agents is progressive once penetration is achieved. Current management of alkaline burn injury is immediate irrigation of the affected area with a continuous flow of water, which should be maintained for at least 2 hours or longer if needed for symptomatic relief. Large wounds, or wounds associated with damage to underlying structures such as tendons or nerves, require additional reconstructive surgery. Recently, it was found experimentally that neutralization of alkaline wounds demonstrated a more rapid return to physiologic pH, less-severe tissue damage, and improved wound healing in comparison to those wounds treated with water.

Hydrofluoric and sulfuric acid are common agents that cause skin injury from acidic solution exposure. The effect an acid has on the skin is determined by the concentration, duration of contact, amount, and penetrability.



A hydrofluoric acid burn of the hand

Hydrofluoric acid is a colorless, fuming liquid that has a highly corrosive effect on skin, causing extensive liquefactive necrosis and severe pain. 27 Deep tissue injury may result, damaging nerves, blood vessels, tendons, and bone. The initial treatment after contact with the skin is copious irrigation, which must be continued for at least 15 to 30 minutes with either water or normal saline. The second aspect of treatment aims to inactivate the free fluoride ion by promoting the formation of an insoluble fluoride salt. Many topical therapies have been advocated and their role in treatment largely anecdotal. Topical quaternary ammonium compounds are still widely used. 29 Topical calcium carbonate gel has been shown to detoxify the fluoride ion and relieve pain. 30,31 The treatment involves massage of a 2.5% calcium carbonate gel into the area of exposure for at least 30 minutes. 32 Some investigators advocate continuing this treatment six times per day for 4 days. 33

Sulfuric acid exposure can cause full-thickness tissue necrosis. Treatment after exposure is immediate copious irrigation of the affected area. This dilutes and removes the sulfuric acid while returning the skin to a normal pH.

Intravenous fluid that extravasates into the peripheral tissues during a venous infusion is a common problem. Intravenous fluid (IVF) extravasation is defined as leakage of injectable fluids out of the vein into the interstitial space. This problem may be the result of a displacement of the IV line or from increased vascular permeability. Depending on the solution being injected, surrounding tissue may be injured to varying degrees. The most common substances that extravasate are cationic solutions (e.g., potassium ion, calcium ion, bicarbonate), osmotically active chemicals (e.g., total parenteral nutrition or hypertonic dextrose solutions), and antibiotics and cytotoxic drugs. Patients undergoing chemotherapy have a 4.7% risk for developing extravasation. 36 In children, the incidence is increased to 11 to 58%. 37 The dorsum of the hand is the most common site of extravasation in the adult, which may result in exposed extensor tendons and loss of function. Other common sites include the antecubital fossa and dorsum of foot and scalp in neonates. The most common intravenous fluid extravasations causing necrosis in the infant are high-concentration dextrose solutions, calcium, bicarbonate, and parenteral nutrition. Newborn babies are at risk because of the fragility and small caliber of their veins, their poor ability to verbalize their pain, and the system of delivery, which pumps the intravenous fluid under pressure.

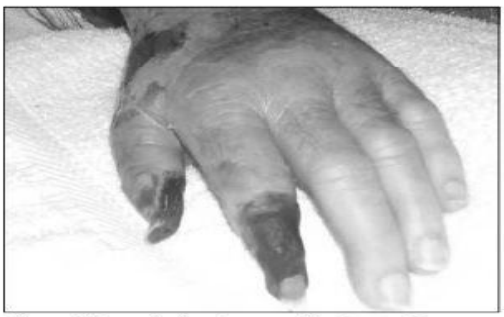


Figure 2. Promethazine Extravasation Causes Gangrene in Man's Fingers. Image provided courtesy of ISMP.

Extravasation causes tissue necrosis either from chemical toxicity, osmotic toxicity, or from the effects of pressure in a closed environment. In most instances, the tissue necrosis is underestimated. Commonly infused drugs that extravasate in adult patients are the

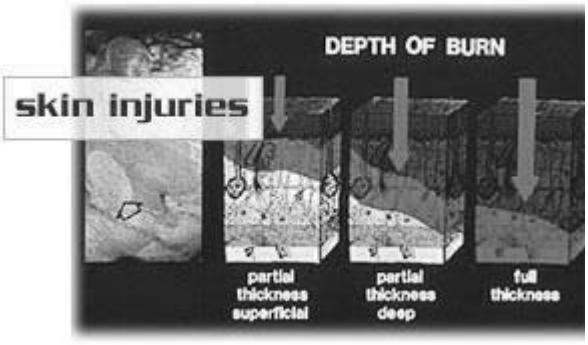
chemotherapeutic agents doxorubicin (Adriamycin) and paclitaxel. 39 The direct toxic effects of doxorubicin on living cells cause cellular death that is perpetuated by the release of doxorubicin-DNA complexes from dead cells. This cellular death prevents the release of cytokines and growth factors, which results in the failure of activation of the cells important in wound healing. Following extravasation, edema, erythema, and induration are usually present with variable amounts of necrotic tissue, the extent of which is not readily apparent. Along with the soft-tissue defect, the limb is also subject to an alteration in function. Injury to underlying nerves, muscles, tendons, and blood vessels must be taken into account. When the extravasation is in proximity to a major artery in the forearm or leg, that extremity is at great risk for amputation. Treatment options vary from early débridement to observation. 42 Gault described a percutaneous saline flush-out technique for both neonates and cancer patients. This involves vigorous liposuction with a small cannula introduced through a small incision adjacent to the area of extravasation. The area is then flushed thoroughly with saline, which is allowed to egress through small stab wounds. 43 This has proved to be useful in acute exacerbations, while patients who present more than 24 hour after extravasation do not benefit from flush-out. Although many options of treatment are available, many investigators have found that an expectant approach is successful in treating the vast majority of patients with extravasation injuries. 39,44 Surgery is limited to those patients with necrotic tissue, pain, or damage of underlying structures such as tendons or nerves.

Translation

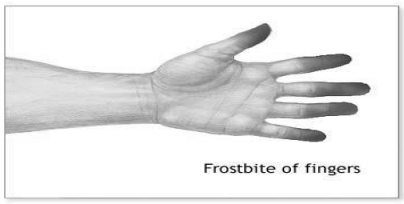
Temperature

Skin exposed to extremes of temperature is at risk of injury. These include hypo- or hyperthermic injuries.

Hyperthermic injury (burns) cause varying degrees of tissue injury, depending on the temperature and length of exposure. Tissue is damaged from heat coagulation in the zone of coagulation, which becomes necrotic tissue. Surrounding the zone of coagulation is the zone of stasis, which has marginal tissue perfusion and questionable viability. The zone of hyperemia is closest to the normal tissue and represents the tissue's response to injury with an increase in blood flow. Burn wounds are covered in greater detail in Chap. 7.



Hypothermia is defined as a core body temperature of less than 35°C (95°F). 45 Frostbite is defined as the acute freezing of tissues. Frostbite severity is related to the duration of exposure and to the temperature gradient at the skin surface. 46 It has been shown experimentally that the tensile strength of a healing wound decreases by 20% in a cold (12°C [53.6°F]) wound environment. Severe hypothermia primarily affects the vasculature as the blood vessels become severely injured by a combination of direct cellular injury and microvascular thrombosis.



McCauley and coworkers have outlined the treatment protocol for frostbite, which includes rapid rewarming, close observation, elevation and splinting, daily hydrotherapy, and serial débridements.

Exposure

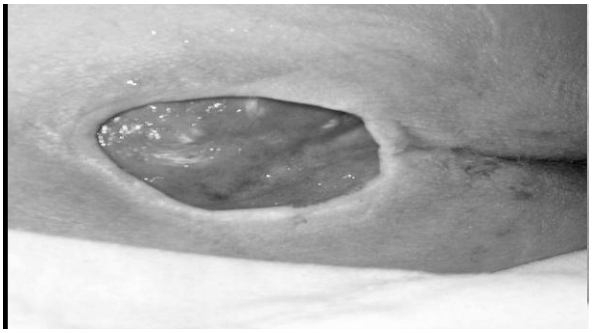
The source of radiation includes an industrial accident that results in an acute injury, therapeutic radiation for the treatment of malignancy, and chronic radiation injury such as solar (ultraviolet) and occupational exposure.

Unit 6: Skin injuries

Reading 1

Decubitus Ulcers (Pressure Ulcers)

Pressure ulcers, as the name implies, are caused by excessive, unrelieved pressure. In animal studies, 60 mm Hg of pressure applied to the skin for 1 hour produces histologically identifiable injuries such as venous thrombosis, muscle degeneration, and tissue necrosis. 48 Normal arteriole, capillary, and venule pressures are 32, 20, and 12 mm Hg, respectively.

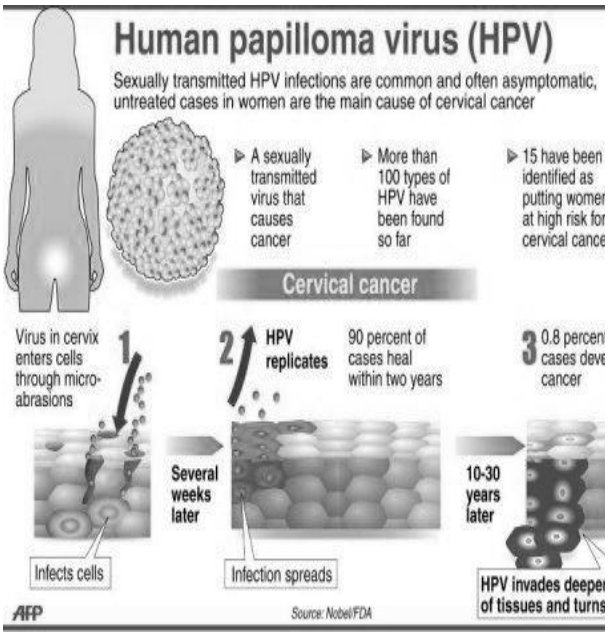


Pressure generated under the ischial tuberosities while a person is seated can reach 300 mm Hg, and sacral pressure can range from 100 to 150 mm Hg while a person lies on a standard hospital mattress. 50 Healthy individuals regularly shift their body weight, even while asleep. Sitting in one position for extended periods of time causes pain via increased pressure in certain areas; this, in turn, stimulates the initiation of movement. Patients unable to sense pain or to shift their body weight, such as paraplegics or bedridden individuals, develop prolonged elevated tissue pressures, and, eventually, necrosis. Muscle tissue is more sensitive to ischemia than the overlying skin. Therefore, the necrotic area is usually wider and deeper than it appears on first inspection.

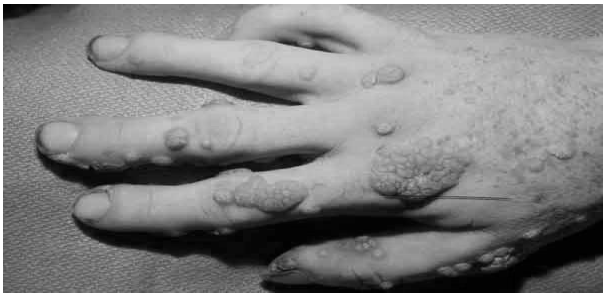
Treatment of pressure sores requires relief of pressure with special cushions and beds and nutritional support to promote healing. The necrotic tissue should be removed, often along with the underlying bony prominence. Shallow ulcers may close by secondary intention, but deeper wounds with involvement of the underlying bone require surgical débridement and coverage. To prevent future breakdown of the area, stable coverage should be obtained with local musculocutaneous or fasciocutaneous flaps. Prevention of ulcers is best achieved by close attention to susceptible areas and frequent repositioning of paralyzed patients. Air flotation mattresses and gel seat cushions redistribute pressure, decrease the incidence of pressure ulcers, and are cost-effective in the care of patients at high risk. The addition of growth factors to these wounds has been found to increase healing and offers promising future therapeutic uses.

Human Papillomavirus

Warts are epidermal growths associated with human papillomavirus (HPV) infection. Histologically they are characterized by hyperkeratosis (hypertrophy of the horny layer), acanthosis (hypertrophy of the spinous layer), and papillomatosis. Koilocytes, which are large keratinocytes with eccentric nuclei, are present.

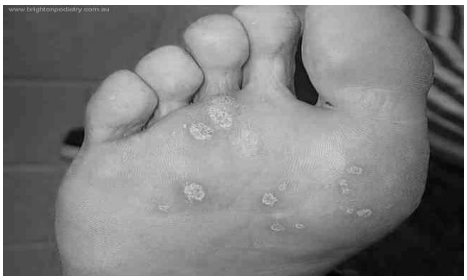


Different morphologic types have a propensity to occur on different parts of the body. The common wart (verruca vulgaris) is found on the fingers and toes, and has a rough, gray-brown surface.



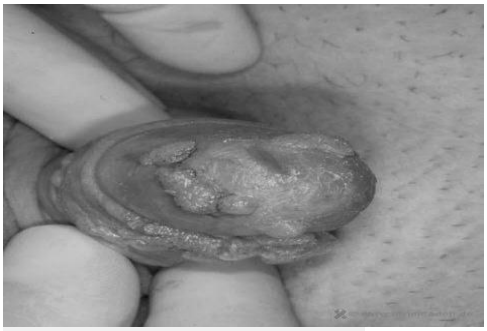
Dermatology Glossary: define your skin missinglink.ucsf.edu600 × 389Search by image Clinical: verruca vulgaris

Plantar warts (verruca plantaris) occur on the soles and palms, and may look like a callus. Flat warts (verruca plana), which are flat but slightly raised, appear on the face, legs, and hands. Venereal warts (condylomata acuminata) grow in the moist areas around the vulva, anus, and scrotum.



Warts can be removed by a number of chemicals, including formalin, podophyllum, and phenol-nitric acid. Curettage with electrodesiccation also can be used for scattered lesions. Treatment of extensive areas of skin requires surgical excision under general anesthesia. 91 Because of the infectious etiology, recurrences are common, and repeated excisions often are necessary to eliminate lesions. Some warts (especially human papillomavirus types 5, 8, and 10) are associated with squamous cell cancers, therefore lesions that grow rapidly or ulcerate should be biopsied. 92

Condylomata acuminata is now one of the most common sexually transmitted viral infections and is largely HPV types 6 and 11. Patients with human immunodeficiency virus (HIV) infection are more likely to develop clinically significant venereal warts. The lesions often are multiple and can grow large in size (Buschke-Löwenstein tumor). Small lesions can be treated with podophyllotoxin cream. Larger lesions have a significant risk of malignant transformation and should be excised. The lesions often recur. Adjuvant therapy with interferon, isotretinoin, or autologous tumor vaccine decreases recurrence rates.

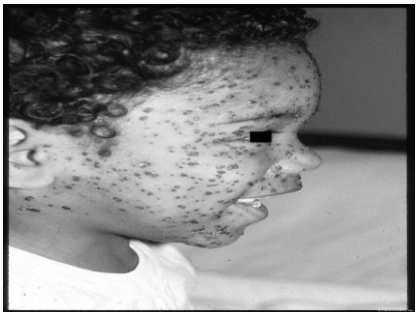

Condylomata acuminata - HIV und A

Immune response modifiers, such as imiquimod, currently show the greatest promise in treating HPV-induced anogenital lesions, both with respect to complete response and in preventing recurrence.

Reading 2

Human Immunodeficiency Virus

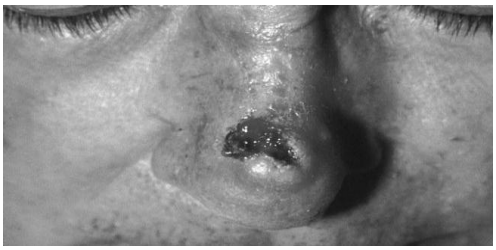
Patients infected with HIV commonly display skin manifestations of their disease. Immune deficiency can occur as a result of infectious processes such as HIV, which causes acquired immunodeficiency syndrome (AIDS), or secondary to immunosuppressive medications, as is the case for transplant recipients. Frequently, people with HIV develop chronic wounds, which become problem wounds given their intrinsic wound-healing deficiencies.



The risk of surgical wound complications increases with the progression of the disease. Many studies have shown a greater incidence of poor wound healing following laparotomy, anorectal surgery, and orthopedic surgery. 96–98 The cause for delayed wound healing is unknown but is thought to be secondary to a decreasing T-cell $CD4^+$ count, presence of an opportunistic infection, low serum albumin, and poor nutrition. 99 Davis and Wastell showed that when comparing biomechanical parameters in the wounds of 11 patients with HIV to those of 11 patients with age-matched control wounds, the wounds of the HIV patients had a lower resilience, toughness, and maximum extension than did the wounds of the control group. These parameters describe the properties of tissues using a tensiometer to determine how the wounds responded to load and deformation. *Resilience* describes the ability of tissue to endure loads without inducing a tension exceeding the elastic limit; *toughness* is the property of tissue that enables it to endure loads; and *maximum extension* is the displacement of the tissue at the point of wound rupture. The overall weakened ability of wound healing in the HIV patient is a consequence of an impairment of the underlying healing process that results in collagen deposition and cross-linking. 100

Malignant Tumors

The most common cancers of the skin arise from the cells of the epidermis and are, in order of frequency, basal cell carcinoma, squamous cell carcinoma, and melanoma. 124 Malignancies arising from cells of the dermis or adnexal structures are much less common.



Environmental influences and concomitant diseases are associated with an increased incidence of epidermal malignancies. These factors have been extensively studied and

form some of our best understanding about the causes of cancer.

Epidemiology

Increased exposure to ultraviolet radiation is associated with an increased development of all three of the common skin malignancies. 125 Epidemiologic studies have shown that people with outdoor occupations have skin malignancies more often than people who work indoors. Squamous cell cancer is much more common on the lower lip than the upper. People with fair complexions are more prone to skin cancer. 126 These same people also are more likely to develop malignancies if they live in areas of the world that receive more sunlight, such as New Zealand, as compared to Great Britain. Albino individuals of dark-skinned races are prone to develop cutaneous neoplasms that usually are rare in the nonalbino members, suggesting that melanin has a large role in protection from carcinogenesis.

Other factors associated with skin malignancies also have been identified. Chemical carcinogens have long been known. In the eighteenth century, Sir Percival Pott noted the association of soot and scrotal cancer in chimney sweeps. Tar, arsenic, and nitrogen mustard are known carcinogens. 128 Human papillomavirus has been found in certain squamous cell cancers and may be linked with oncogenesis. 129 Radiation therapy in the past for skin lesions such as acne vulgaris, when it resulted in radiation dermatitis, is associated with an increased incidence of basal and squamous cell cancers in the treated areas. Any area of skin subjected to chronic irritation, such as burn scars (Marjolin's ulcers), repeated sloughing of skin from bullous diseases, and decubitus ulcers, all have an increased chance of developing squamous cell cancer. 130,131 A variant of this type of lesion develops on skin that has suffered repeated burns.

Systemic immunologic dysfunction is related to an increase in cutaneous malignancies. Immunosuppressed patients receiving chemotherapy for other malignancies or immunosuppressants for organ transplants have an increased incidence of basal cell and squamous cell cancers and malignant melanoma. AIDS is associated with an increased risk of developing skin neoplasms. 132 Patients with HIV should be monitored vigilantly for signs of skin cancer.

Translation

Opioid Analgesics

Opioids are the most potent pain-relieving drugs currently available. Of all analgesics, they have the broadest range of efficacy and provide the most reliable and effective method for rapid pain relief. Although side effects are common, most are reversible: nausea, vomiting, pruritus, and constipation are the most frequent and bothersome side effects. Respiratory depression is uncommon at standard analgesic doses, but can be life-threatening. Opioid-related side effects can be reversed rapidly with the narcotic antagonist naloxone. The physician should not hesitate to use opioid analgesics in patients with acute severe pain.

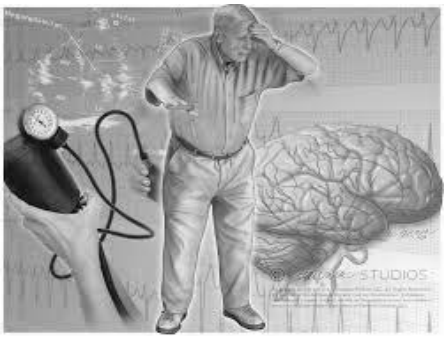
Opioids produce analgesia by actions in the CNS. They activate pain-inhibitory neurons and directly inhibit pain-transmission neurons. Most of the commercially available opioid analgesics act at the same opioid receptor (-receptor), differing mainly in potency, speed of onset, duration of action, and optimal route of administration. Some side effects are due to accumulation of nonopioid metabolites that are unique to individual drugs. One striking example of this is normeperidine, a metabolite of meperidine. Normeperidine produces hyperexcitability and seizures that are not reversible with naloxone. Normeperidine accumulation is increased in patients with renal failure.

Unit 7: Syncope

Reading 1

Introduction

Syncope is a transient, self-limited loss of consciousness due to acute global impairment of cerebral blood flow. The onset is rapid, duration brief, and recovery spontaneous and complete. Other causes of transient loss of consciousness need to be distinguished from syncope; these include seizures, vertebrobasilar ischemia, hypoxemia, and hypoglycemia. A syncopal prodrome (*presyncope*) is common, although loss of consciousness may occur without any warning symptoms. Typical presyncopal symptoms include dizziness, lightheadedness or faintness, weakness, fatigue, and visual and auditory disturbances. The causes of syncope can be divided into three general categories: (1) neurally mediated syncope (also called *reflex syncope*), (2) orthostatic hypotension, and (3) cardiac syncope.



Neurally mediated syncope comprises a heterogeneous group of functional disorders that are characterized by a transient change in the reflexes responsible for maintaining cardiovascular homeostasis. Episodic vasodilation and bradycardia occur in varying combinations, resulting in temporary failure of blood pressure control. In contrast, in patients with orthostatic hypotension due to autonomic failure, these cardiovascular homeostatic reflexes are chronically impaired. Cardiac syncope may be due to arrhythmias or structural cardiac diseases that cause a decrease in cardiac output. The clinical features, underlying pathophysiologic mechanisms, therapeutic interventions, and prognoses differ markedly among these three causes.

Epidemiology and Natural History

Syncope is a common presenting problem, accounting for approximately 3% of all emergency room visits and 1% of all hospital admissions. The annual cost for syncope-related hospitalization in the United States is ~ $2 billion. Syncope has a lifetime cumulative incidence of up to 35% in the general population. The peak incidence in the young occurs between ages 10 and 30 years, with a median peak around 15 years. Neurally mediated syncope is the etiology in the vast majority of these cases. In elderly adults, there is a sharp rise in the incidence of syncope after 70 years.

In population-based studies, neurally mediated syncope is the most common cause of syncope. The incidence is slightly higher in females than males. In young subjects there is often a family history in first-degree relatives. Cardiovascular disease due to structural disease or arrhythmias is the next most common cause in most series, particularly in emergency room settings and in older patients. Orthostatic hypotension also increases in prevalence with age because of the reduced baroreflex responsiveness, decreased cardiac compliance, and attenuation of the vestibulosympathetic reflex associated with aging. In the elderly, orthostatic hypotension is substantially more common in institutionalized (54–68%) than community dwelling (6%) individuals, an observation most likely explained by the greater prevalence of predisposing neurologic

disorders, physiologic impairment, and vasoactive medication use among institutionalized patients.

The prognosis after a single syncopal event for all age groups is generally benign. In particular, syncope of noncardiac and unexplained origin in younger individuals has an excellent prognosis; life expectancy is unaffected. By contrast, syncope due to a cardiac cause, either structural heart disease or primary arrhythmic disease, is associated with an increased risk of sudden cardiac death and mortality from other causes. Similarly, mortality rate is increased in individuals with syncope due to orthostatic hypotension related to age and the associated comorbid conditions (Table 20-1).

Table 20-1 High-Risk Features Indicating Hospitalization or Intensive Evaluation of Syncope
Chest pain suggesting coronary ischemia
Features of congestive heart failure
Moderate or severe valvular disease
Moderate or severe structural cardiac disease
Electrocardiographic features of ischemia
History of ventricular arrhythmias
Prolonged QT interval (>500 msec)
Repetitive sinoatrial block or sinus pauses
Persistent sinus bradycardia
Trifascicular block
Atrial fibrillation
Nonsustained ventricular tachycardia
Family history of sudden death
Preexcitation syndromes
Brugada pattern on ECG

Pathophysiology

The upright posture imposes a unique physiologic stress upon humans; most, although not all, syncopal episodes occur from a standing position. Standing results in pooling of 500–1000 mL of blood in the lower extremities and splanchnic circulation. There is a decrease in venous return to the heart and reduced ventricular filling that result in diminished cardiac output and blood pressure. These hemodynamic changes provoke a compensatory reflex response, initiated by the baroreceptors in the carotid sinus and aortic arch, resulting in increased sympathetic outflow and decreased vagal nerve activity (Fig. 20-1). The reflex increases peripheral resistance, venous return to the heart, and cardiac output and thus limits the fall in blood pressure. If this response fails, as is the case chronically in orthostatic hypotension and transiently in neurally mediated syncope, cerebral hypoperfusion occurs.

Dizziness and Vertigo

Dizziness is a common, vexing symptom, and epidemiologic data indicate that more than 20% of adults experience dizziness within a given year. The diagnosis is frequently challenging, in part because patients use the term to refer to a variety of different sensations, including feelings of faintness, spinning, and other illusions of motion, imbalance, and anxiety. Other descriptive words, such as *light-headedness*, are equally ambiguous, referring in some cases to a presyncopal sensation due to hypoperfusion of the brain and in others to disequilibrium and imbalance. Patients often have difficulty distinguishing among these various symptoms, and the words they choose do not describe the underlying etiology reliably.

Vascular disorders cause presyncopal dizziness as a result of cardiac dysrhythmia, orthostatic hypotension, medication effects, or another cause. Such presyncopal sensations vary in duration; they may increase in severity until loss of consciousness occurs, or they may resolve before loss of consciousness if the cerebral ischemia is corrected. Faintness and syncope, which are discussed in detail in Chap. 20, should always be considered when one is evaluating patients with brief episodes of dizziness or dizziness that occurs with upright posture.

Vestibular causes of dizziness may be due to peripheral lesions that affect the labyrinths or vestibular nerves or to involvement of the central vestibular pathways. They may be paroxysmal or due to a fixed unilateral or bilateral vestibular deficit. Acute unilateral lesions cause vertigo due to a sudden imbalance in vestibular inputs from the two labyrinths. Bilateral lesions cause imbalance and instability of vision when the head moves (*oscillopsia*). Other causes of dizziness include nonvestibular imbalance and gait disorders (e.g., loss of proprioception from sensory neuropathy, parkinsonism) and anxiety.

In evaluating patients with dizziness, questions to consider include the following: (1) is it dangerous (e.g., arrhythmia, transient ischemic attack/stroke)? (2) is it vestibular? and (3) if vestibular, is it peripheral or central? A careful history and examination often provide enough information to answer these questions and determine whether additional studies or referral to a specialist is necessary.

Reading 2

Approach to the Patient: Dizziness

When a patient presents with dizziness, the first step is to delineate more precisely the nature of the symptom. In the case of vestibular disorders, the physical symptoms depend on whether the lesion is unilateral or bilateral and whether it is acute or chronic and progressive. Vertigo, an illusion of self or environmental motion, implies asymmetry of vestibular inputs from the two labyrinths or in their central pathways and is usually acute. Symmetric bilateral vestibular hypofunction causes imbalance but no vertigo. Because of the ambiguity in patients' descriptions of their symptoms, diagnosis based simply on symptom character is typically unreliable. The history should focus closely on other features, including whether dizziness is paroxysmal or has occurred only once, the duration of each episode, any provoking factors, and the symptoms that accompany the dizziness.

Causes of dizziness can be divided into episodes that last for seconds, minutes, hours, or days. Common causes of brief dizziness (seconds) include benign paroxysmal positional vertigo (BPPV) and orthostatic hypotension, both of which typically are provoked by changes in position. Attacks of migrainous vertigo and Ménière's disease often last hours. When episodes are of intermediate duration (minutes), transient ischemic attacks of the posterior circulation should be considered, although these episodes also could be due to migraine or a number of other causes.

Symptoms that accompany vertigo may be helpful in distinguishing peripheral vestibular lesions from central causes. Unilateral hearing loss and other aural symptoms (ear pain,

pressure, fullness) typically point to a peripheral cause. Because the auditory pathways quickly become bilateral upon entering the brainstem, central lesions are unlikely to cause unilateral hearing loss (unless the lesion lies near the root entry zone of the auditory nerve). Symptoms such as double vision, numbness, and limb ataxia suggest a brainstem or cerebellar lesion.

Examination

Because dizziness and imbalance can be a manifestation of a variety of neurologic disorders, the neurologic examination is important in the evaluation of these patients. Particular focus should be given to assessment of eye movements, vestibular function, and hearing. The range of eye movements and whether they are equal in each eye should be observed. Peripheral eye movement disorders (e.g., cranial neuropathies, eye muscle weakness) are usually *disconjugate* (different in the two eyes). One should check pursuit (the ability to follow a smoothly moving target) and saccades (the ability to look back and forth accurately between two targets). Poor pursuit or inaccurate (*dysmetric*) saccades usually indicates central pathology, often involving the cerebellum. Finally, one should look for spontaneous nystagmus, an involuntary back-and-forth movement of the eyes. Most often nystagmus is of the jerk type, in which a slow drift (*slow phase*) in one direction alternates with a rapid saccadic movement (*quick phase* or *fast phase*) in the opposite direction that resets the position of the eyes in the orbits. Table 21-1 lists features that help distinguish peripheral vestibular nystagmus from central nystagmus. Except in the case of acute vestibulopathy (e.g., vestibular neuritis), if primary position nystagmus is easily seen in the light, it is probably due to a central cause. Two forms of nystagmus that are characteristic of lesions of the cerebellar pathways are vertical nystagmus with downward fast phases (downbeat nystagmus) and horizontal nystagmus that changes direction with gaze (gaze-evoked nystagmus).

Translation

Headache is among the most common reasons patients seek medical attention. Diagnosis and management is based on a careful clinical approach augmented by an understanding of the anatomy, physiology, and pharmacology of the nervous system pathways that mediate the various headache syndromes.

General Principles

A classification system developed by the International Headache Society characterizes headache as primary or secondary. *Primary headaches* are those in which headache and its associated features are the disorder in itself, whereas *secondary headaches* are those caused by exogenous disorders. Primary headache often results in considerable disability and a decrease in the patient's quality of life. Mild secondary headache, such as that seen in association with upper respiratory tract infections, is common but rarely worrisome. Life-threatening headache is relatively uncommon, but vigilance is required in order to recognize and appropriately treat such patients.

Anatomy and Physiology of Headache

Pain usually occurs when peripheral nociceptors are stimulated in response to tissue injury, visceral distension, or other factors (Chap. 11). In such situations, pain perception is a normal physiologic response mediated by a healthy nervous system. Pain can also result when pain-producing pathways of the peripheral or central nervous system (CNS) are damaged or activated inappropriately. Headache may originate from either or both mechanisms. Relatively few cranial structures are pain-producing; these include the scalp, middle meningeal artery, dural sinuses, falx cerebri, and proximal segments of the large pial arteries. The ventricular ependyma, choroid plexus, pial veins, and much of the brain parenchyma are not pain-producing.

The key structures involved in primary headache appear to be

- the large intracranial vessels and dura mater and the peripheral terminals of the trigeminal nerve that innervate these structures
- the caudal portion of the trigeminal nucleus, which extends into the dorsal horns of the upper cervical spinal cord and receives input from the first and second cervical nerve roots (the trigeminocervical complex)
- rostral pain-processing regions, such as the ventroposteromedial thalamus and the cortex
- the pain-modulatory systems in the brain that modulate input from trigeminal nociceptors at all levels of the pain-processing pathways

The innervation of the large intracranial vessels and dura mater by the trigeminal nerve is known as the *trigeminovascular system*. Cranial autonomic symptoms, such as *lacrimation* and *nasal congestion*, are prominent in the trigeminal autonomic cephalalgias, including cluster headache and paroxysmal hemicrania, and may also be seen in migraine. These autonomic symptoms reflect activation of cranial parasympathetic pathways, and functional imaging studies indicate that vascular changes in migraine and cluster headache, when present, are similarly driven by these cranial autonomic systems. Migraine and other primary headache types are not "vascular headaches"; these disorders do not reliably manifest vascular changes, and treatment outcomes cannot be predicted by vascular effects. Migraine is a brain disorder, and best understood and managed as such.

Clinical Evaluation of Acute, New-Onset Headache

The patient who presents with a new, severe headache has a differential diagnosis that is quite different from the patient with recurrent headaches over many years. In new-onset and severe headache, the probability of finding a potentially serious cause is considerably greater than in recurrent headache. Patients with recent onset of pain require prompt evaluation and appropriate treatment. Serious causes to be considered include meningitis, subarachnoid hemorrhage, epidural or subdural hematoma, glaucoma, tumor, and purulent sinusitis. When worrisome symptoms and signs are present (Table 14–2), rapid diagnosis and management is critical.

Table 14-2 Headache Symptoms that Suggest a Serious Underlying Disorder

"Worst" headache ever
First severe headache
Subacute worsening over days or weeks
Abnormal neurologic examination
Fever or unexplained systemic signs
Vomiting that precedes headache
Pain induced by bending, lifting, cough
Pain that disturbs sleep or presents immediately upon awakening
Known systemic illness
Onset after age 55
Pain associated with local tenderness, e.g., region of temporal artery

A complete neurologic examination is an essential first step in the evaluation. In most cases, patients with an abnormal examination or a history of recent-onset headache should be evaluated by a CT or MRI study. As an initial screening procedure for intracranial pathology in this setting, CT and MRI methods appear to be equally sensitive. In some circumstances, a lumbar puncture (LP) is also required, unless a benign etiology can be otherwise established. A general evaluation of acute headache might include the investigation of cardiovascular and renal status by blood pressure monitoring and urine examination; eyes by funduscopy, intraocular pressure measurement, and refraction; cranial arteries by palpation; and cervical spine by the effect of passive movement of the head and by imaging.

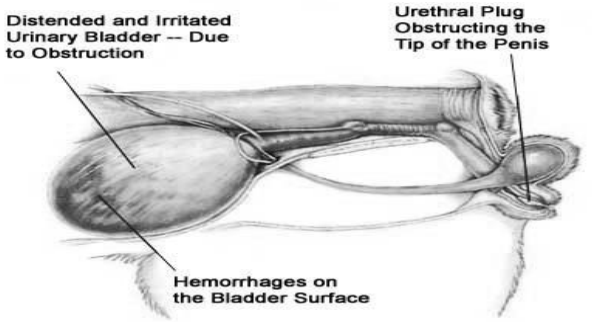
The psychological state of the patient should also be evaluated since a relationship exists between head pain and depression. Many patients in chronic daily pain cycles become depressed, although depression itself is rarely a cause of headache. Drugs with antidepressant actions are also effective in the prophylactic treatment of both tension-type headache and migraine.

Unit 8: Urology

Reading 1

Symptoms Related to Voiding

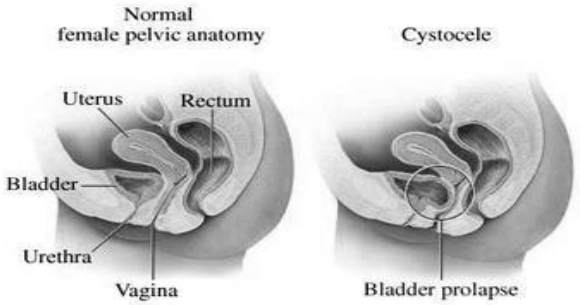
Symptoms related to voiding can be broadly categorized as irritative or obstructive. Specific irritative symptoms include dysuria, frequency, and urgency. These symptoms generally imply inflammation of the urethra, prostate, or bladder. Although irritative voiding symptoms are commonly caused by infection, they can also be caused by malignancy, and in patients with symptoms that persist after treatment with appropriate antibiotics, malignant processes such as transitional cell carcinoma must be ruled out. In symptomatic patients with no specific etiology, the diagnosis of interstitial cystitis or chronic nonbacterial prostatitis is often made. The pathophysiology of both these processes is poorly understood and results of available treatments are often unsatisfactory.



Specific obstructive voiding symptoms include a weak urinary stream, urgency, frequency, hesitancy, intermittency, nocturia, and sense of incomplete emptying. Hesitancy refers to a delay in initiating a urinary stream and intermittency refers to repeated starting and stopping of the urine stream during voiding. The most common cause of obstructive voiding in men is benign prostatic hyperplasia. Urethral strictures may also obstruct the bladder outlet and are often secondary to trauma, urethritis or previous instrumentation of the bladder.

Urinary Incontinence

Urinary incontinence can be categorized as stress, urge, total, and overflow. Stress incontinence refers to incontinence associated with an increase in intra-abdominal pressure. Patients often report leakage of urine when coughing, laughing, or during physical exertion. Stress incontinence is secondary to a decrease in the resistance provided by the urinary continence mechanisms and generally implies an anatomic disorder, such as an iatrogenic injury to the external sphincter in a male or prolapse of the bladder in a female. Urge incontinence is secondary to an involuntary contraction of the bladder and is accompanied by a sudden sense of needing to void. Urge incontinence may be secondary to inflammation and irritation of the bladder, or it may result from neurologic disorders such as a stroke or spinal cord injury.

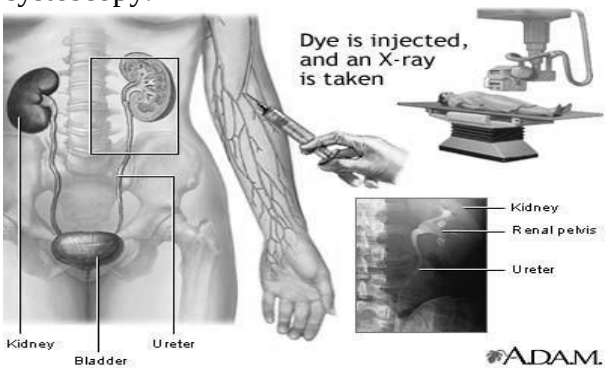


Total incontinence refers to a continuous leakage of urine and implies a fistula between the skin or vagina and the urinary tract, proximal to the sphincter mechanism. Women with a vesicovaginal fistula secondary to malignancy or trauma will complain of continuous leakage of urine. Overflow incontinence is secondary to an obstruction of the lower urinary tract. As urine builds up in the bladder, the intravesical pressure increases and overcomes the resistance provided by the urinary sphincter. All patients at risk for urinary tract obstruction who develop new-

onset incontinence should be checked for urinary retention by postvoid bladder ultrasound or catheterization of the bladder.

Hematuria

Patients with gross or microscopic hematuria, in the absence of obvious evidence of a urinary tract infection, need to be evaluated with upper and lower tract studies. On microscopic examination of the urine, more than five red blood cells per high power field in spun urine or more than two red blood cells per high power field in unspun urine is considered significant microscopic hematuria. Because hematuria can be intermittent, even a single documented episode of significant microscopic hematuria warrants a complete evaluation. The upper tract, which includes the kidney and ureter, should be evaluated with an intravenous pyelogram, CT scan, or retrograde pyelogram. The CT scan should be performed with intravenous contrast and delayed images should be obtained once the excreted contrast has filled the upper tract collecting system. The lower tract, which includes the bladder and urethra, should be evaluated by cystoscopy.



The differential diagnosis for hematuria includes malignancies, infections, kidney stones, and trauma. Malignancies of the kidney and bladder classically present with painless hematuria. Patients with gross painless hematuria should be considered to have a urinary tract malignancy until proven otherwise. Infections involving the bladder or urethra are generally associated with symptoms of irritative voiding. Pyelonephritis is a clinical diagnosis based on findings of irritative voiding symptoms, fever, and flank pain. Kidney stones are associated with a colicky pain. The localization of the pain depends on the level of obstruction by the stone. An obstruction at the ureteropelvic junction will cause flank pain while obstruction of the lower ureter can produce colicky pain referred to the lower abdomen or groin.

Other Findings

Other complaints and findings related to the urinary system include urethral discharge, hematospermia, and pneumaturia. Urethral discharge is a common complaint that usually results from infection with *Neisseria gonorrhoeae* or *Chlamydia trachomatis*. The discharge is often associated with dysuria. Hematospermia refers to blood in the ejaculated semen and is caused by inflammation of seminal vesicles or prostate. As a general rule, hematospermia is self-limiting and does not require further evaluation or treatment. Pneumaturia refers to air in the voided urine. The finding of pneumaturia can be confirmed by having the patient void in a tub with the urethral meatus submerged. Pneumaturia may result from recent instrumentation of the bladder or from a fistula between the urinary tract and the intestine.

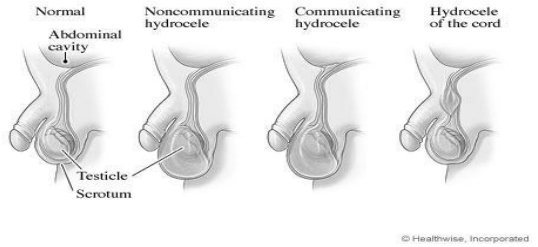
Reading 2

Physical Examination of the Penis, Scrotum, and Testis

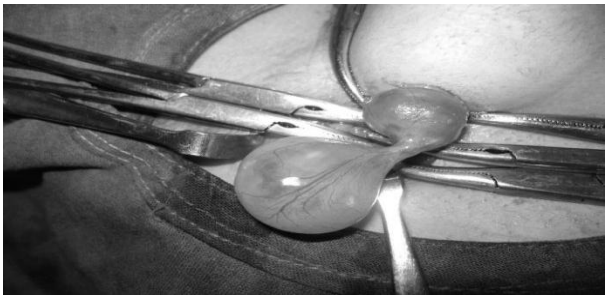
The physical examination of a male patient should be performed with the patient standing and the physician seated on a stool. Initially, the skin of the penis, scrotum, and the surrounding inguinal region should be visually inspected. The testicles should be palpated for

masses or tenderness and the size of the testicles should be noted. The epididymis can be palpated on the posterolateral surface of the testicles. Any nodules should be noted and an effort should be made to determine if palpable lesions are associated with the testis or the epididymis. The vas deferens can be felt by gently compressing the scrotum above the testicles.

Hydroceles represent a buildup of fluid between the two layers of the tunica vaginalis. If the testicles are enlarged by a hydrocele, the presence of a hydrocele sac can be confirmed by transilluminating the sac with a penlight.

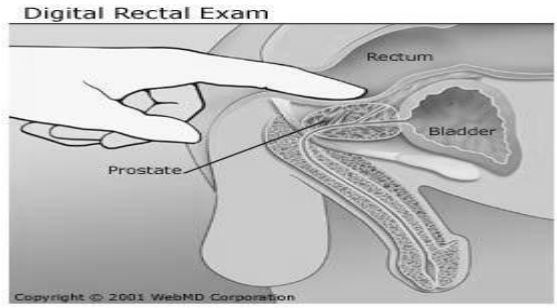


Varicoceles may be palpable in the scrotum and represent dilated veins, which are analogous to varicose veins found on the leg. The penis should be gently massaged to express any urethral discharge. The penile shaft and urethra should be palpated along the length of the penis. Any nodules or fibrotic plaques on the corporal bodies should be noted.



Prostate Exam

The prostate is examined with the patient leaning over an examination bench and resting on his elbows. Alternatively, the patient can be lying in a lateral decubitus position. Initially, the anus and surrounding area is visually inspected. Using lubrication, the index finger is gently inserted into the rectum. The prostate is palpated, and any nodules, indurations or asymmetry should be noted. Although the seminal vesicle is too far to reach in most men, they may occasionally be palpable just above the prostate. Having the patient Valsalva will often bring the prostate closer to the anus and facilitate the exam.



Translation

Urinary Tract Infections, Pyelonephritis, and Prostatitis: Introduction

Urinary tract infection (UTI) is a common and painful human illness that, fortunately, is rapidly responsive to modern antibiotic therapy. In the preantibiotic era, UTI caused significant morbidity. Hippocrates, writing about a disease that appears to have been acute cystitis, said that the illness could last for a year before either resolving or worsening to involve the kidneys. When chemotherapeutic agents used to treat UTI were introduced in the early twentieth century, they were relatively ineffective, and persistence of infection after 3 weeks of therapy was common. Nitrofurantoin, which became available in the 1950s, was the first tolerable and effective agent for the treatment of UTI.

Since the most common manifestation of UTI is acute cystitis and since acute cystitis is far more prevalent among women than among men, most clinical research on UTI has involved women. Many studies have enrolled women from college campuses or large health maintenance organizations in the United States. Therefore, when reviewing the literature and recommendations concerning UTI, clinicians must consider whether the findings are applicable to their patient populations.

Definitions

UTI may be asymptomatic (subclinical infection) or symptomatic (disease). Thus, the term *UTI* encompasses a variety of clinical entities, including asymptomatic bacteriuria (ABU), cystitis, prostatitis, and pyelonephritis. The distinction between symptomatic UTI and ABU has major clinical implications. Both UTI and ABU connote the presence of bacteria in the urinary tract, usually accompanied by white blood cells and inflammatory cytokines in the urine. However, ABU occurs in the absence of symptoms attributable to the bacteria in the urinary tract and does not usually require treatment, while UTI has more typically been assumed to imply symptomatic disease that warrants antimicrobial therapy. Much of the literature concerning UTI, particularly catheter-associated infection, does not differentiate between UTI and ABU. In this chapter, the term *UTI* denotes symptomatic disease; *cystitis*, symptomatic infection of the bladder; and *pyelonephritis*, symptomatic infection of the kidneys. *Uncomplicated UTI* refers to acute cystitis or pyelonephritis in nonpregnant outpatient women without anatomic abnormalities or instrumentation of the urinary tract; *complicated UTI* is a catch-all term that encompasses all other types of UTI. *Recurrent UTI* is not necessarily complicated; individual episodes can be uncomplicated and treated as such. *Catheter-associated bacteriuria* can be either symptomatic (CAUTI) or asymptomatic.

Pathogenesis

The urinary tract can be viewed as an anatomic unit united by a continuous column of urine extending from the urethra to the kidneys. In the majority of UTIs, bacteria establish infection by ascending from the urethra to the bladder. Continuing ascent up the ureter to the kidney is the pathway for most renal parenchymal infections. However, introduction of bacteria into the bladder does not inevitably lead to sustained and symptomatic infection. The interplay of host, pathogen, and environmental factors determines whether tissue invasion and symptomatic infection will ensue. For example, bacteria often enter the bladder after sexual intercourse, but normal voiding and innate host defense mechanisms in the bladder eliminate these organisms. Any foreign body in the urinary tract, such as a urinary catheter or stone, provides an inert surface for bacterial colonization. Abnormal micturition and/or significant residual urine volume promotes true infection. In the simplest of terms, anything that increases the likelihood of bacteria entering the bladder and staying there increases the risk of UTI.

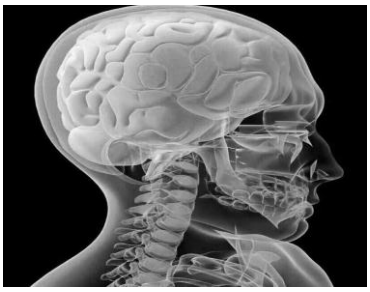
Bacteria can also gain access to the urinary tract through the bloodstream. However, hematogenous spread accounts for <2% of documented UTIs and usually results from bacteremia caused by relatively virulent organisms, such as *Salmonella* and *S. aureus*. Indeed, the isolation of either of these pathogens from a patient without a catheter or other instrumentation warrants a search for a bloodstream source. Hematogenous infections may produce focal abscesses or areas of pyelonephritis within a kidney and result in positive urine cultures. The pathogenesis of candiduria is distinct in that the hematogenous route is common. The presence of *Candida* in the urine of a noninstrumented immunocompetent patient implies either genital contamination or potentially widespread visceral dissemination.

Unit 9: Neurosurgery

Reading 1

Introduction

Neurologic surgery is a discipline of medicine and the specialty of surgery that provides the operative and nonoperative management (i.e., prevention, diagnosis, evaluation, treatment, critical care, and rehabilitation) of disorders of the central, peripheral, and autonomic nervous systems, including their supporting structures and vascular supply; the evaluation and treatment of pathologic processes that modify the function or activity of the nervous system, including the hypophysis; and the operative and nonoperative management of pain. As such, neurologic surgery encompasses the treatment of adult and pediatric patients with disorders of the nervous system.



These disorders include those of the brain, meninges, skull and skull base, and their blood supply, including surgical and endovascular treatment of disorders of the intracranial and extracranial vasculature supplying the brain and spinal cord; disorders of the pituitary gland; disorders of the spinal cord, meninges, and vertebral column, including those that may require treatment by fusion, instrumentation, or endovascular techniques; and disorders of the cranial and spinal nerves throughout their distribution.

An accurate history is the first step toward neurologic diagnosis. A history of trauma or of neurologic symptoms is of obvious interest, but general constitutional symptoms also are important. Neurologic disease may have systemic effects, while diseases of other symptoms may affect neurologic function. The patient's general medical ability to withstand the physiologic stress of anesthesia and surgery should be understood. A detailed history from the patient and/or family, along with a reliable physical examination will clarify these issues.

Neurologic Examination

The neurologic examination is divided into several components and is generally done from head to toe. First assess mental status. A patient may be awake, lethargic (will follow commands and answer questions, but then returns to sleep), stuporous (difficult to arouse at all), or comatose (no purposeful response to voice or pain). Cranial nerves may be thoroughly tested in the awake patient, but pupil reactivity, eye movement, facial symmetry, and gag are the most relevant when mental status is impaired. Motor testing is based on maximal effort of major muscle groups in those able to follow commands, while assessing for amplitude and symmetry of movement to deep central pain may be all that is possible for stuporous patients. Table 41-1 details scoring for motor assessment tests. Characteristic motor reactions to pain in patients with depressed mental status include withdrawal from stimulus, localization to stimulus, flexor (decorticate) posturing, extensor (decerebrate) posturing, or no reaction (in order of worsening pathology).

Figure 41-1 diagrams the clinical patterns of posturing. This forms the basis of determining the Glasgow Coma Scale motor score, as detailed in Table 41-2. Light touch, proprioception, temperature, and pain testing may be useful in awake patients but is often impossible without good cooperation. It is critical to document sensory patterns in spinal cord injury patients. Muscle stretch reflexes should be checked. Often comparing left to right or upper extremity to lower extremity reflexes for symmetry is the most useful for localizing a lesion. Check for ankle-jerk clonus or up-going toes (the Babinski test). Presence of either is pathologic and signifies upper motor neuron disease.

Table 41-1 Motor Scoring System

Grade	Description
0	No muscle contraction
1	Visible muscle contraction without movement across the joint
2	Movement in the horizontal plane, unable to overcome gravity
3	Movement against gravity
4	Movement against some resistance
5	Normal strength

Table 41-2 The Glasgow Coma Scale (GCS) Score[a]

Motor Response (M)		Verbal Response (V)		Eye-Opening Response (E)	
Obeys commands	6	Oriented	5	Opens spontaneously	4
Localizes to pain	5	Confused	4	Opens to speech	3
Withdraws from pain	4	Inappropriate words	3	Opens to pain	2
Flexor posturing	3	Unintelligible sounds	2	No eye opening	1
Extensor posturing	2	No sounds	1		
No movement	1				

Reading 2

Trauma

Trauma is the leading cause of death in children and young adults; however, incidences of death and disability from trauma have been slowly decreasing. This is partly attributable to increased awareness of the importance of using seat belts and bicycle and motorcycle helmets. However, trauma remains a major cause of morbidity and mortality, and can affect every major organ system in the body. The three main areas of neurosurgic interest in trauma are TBI, spine and spinal cord injury (SCI), and peripheral nerve injury.

Scalp Injury

Blunt or penetrating trauma to the head can cause injury to the densely vascularized scalp, and significant blood loss can occur. Direct pressure initially controls the bleeding, allowing close inspection of the injury. If a simple laceration is found, it should be copiously irrigated and closed primarily. If the laceration is short, a single-layer percutaneous suture closure will suffice. If the laceration is long or has multiple arms, the patient may need débridement and closure in the operating room, with its superior lighting and wider selection of instruments and suture materials. Careful reapproximation of the galea will provide a more secure closure and better hemostasis. Blunt trauma can also cause crush injury with subsequent tissue necrosis. These wounds require débridement and consideration of advancement flaps to cover the defect.

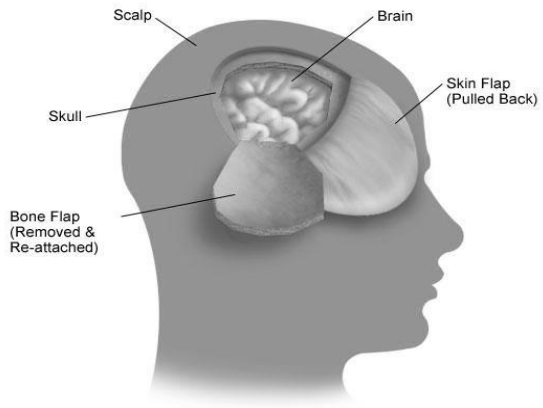
Skull Fractures

The usual classification system for bone fractures may be applied to the skull. Characterization may be done using skull x-rays or head CT. 2 A closed fracture is covered by intact skin. An open, or compound, fracture is associated with disrupted overlying

skin. The fracture lines may be single (linear); multiple and radiating from a point (stellate); or multiple, creating fragments of bone (comminuted). Closed skull fractures do not normally require specific treatment. Open fractures require repair of the scalp. Skull fractures in general indicate that a significant amount of force was transmitted to the head, and should increase the suspicion for intracranial injury. Fractures that cross meningeal arteries can cause rupture of the artery and subsequent epidural hematoma formation.

Depressed skull fractures may result from a focal injury of significant force. The inner and outer cortices of the skull are disrupted, and a fragment of bone is pressed in toward the brain in relation to adjacent intact skull. The fragment may overlap the edge of intact bone, or may plunge completely below the level of adjacent normal skull. The inner cortex of the bone fragments often has multiple sharp edges that can lacerate dura, brain, and vessels. Craniotomy is required to elevate the fracture, repair dural disruption, and obtain hemostasis in these cases (Fig. 41-7). Fractures overlying dural venous sinuses require restraint. Surgical exploration can lead to life-threatening hemorrhage from the lacerated sinus.

Example of a Craniotomy Procedure



A. Bone-window axial head CT of a patient who presented aphasic after being struck with the bottom of a beer bottle. CT demonstrates a depressed skull fracture in the left posterior temporoparietal area. B. Brain-window axial head CT demonstrating intraparenchymal hematoma caused by laceration of cortical vessels by the edge of the fractured bone. Arrowhead indicates traumatic subarachnoid hemorrhage in the sylvian fissure.

Fractures of the skull base are common in head-injured patients, and they indicate significant impacts. They are generally apparent on routine head CT, but should be evaluated with dedicated fine-slice coronal-section CT scan to document and delineate the extent of the fracture and involved structures. If asymptomatic, they require no treatment. Symptoms from skull base fractures include cranial nerve deficits and CSF leaks. A fracture of the temporal bone, for instance, can damage the facial or vestibulocochlear nerve, resulting in vertigo, ipsilateral deafness, or facial paralysis. A communication may be formed between the subarachnoid space and the middle ear, allowing CSF drainage into the pharynx via the eustachian tube or from the ear (otorrhea). Extravasation of blood results in ecchymosis behind the ear, known as Battle's sign. A fracture of the anterior skull base can result in anosmia (loss of smell from damage to the olfactory nerve), CSF drainage from the nose (rhinorrhea), or periorbital ecchymoses, known as raccoon eyes.

Copious clear drainage from the nose or ear makes the diagnosis of CSF leakage obvious. Often, however, the drainage may be discolored with blood or small in volume if some drains into the throat. The halo test can help differentiate. Allow a drop of the fluid to fall on an absorbent surface such as a facial tissue. If blood is mixed with CSF, the drop will form a double ring, with a darker center spot containing blood components surrounded

by a light halo of CSF. If this is indeterminate, the fluid can be sent to the lab for beta-transferrin testing. Beta-transferrin testing will only be positive if CSF is present.

Many CSF leaks will heal with elevation of the head of the bed for several days. A lumbar drain can augment this. A lumbar drain is a catheter placed in the lumbar CSF cistern to decompress the cranial vault and allow the defect to heal by eliminating normal hydrostatic pressure. There is no proven efficacy of antibiotic coverage for preventing meningitis in patients with CSF leaks.

Traumatic cranial neuropathies are generally managed conservatively, with documentation of the extent of impairment and signs of recovery. Patients with traumatic facial nerve palsies may benefit from a course of steroids, although their benefit is unproven. Patients with facial nerve palsy of abrupt onset, who do not respond to steroids within 48 to 72 hours may be considered for surgical decompression of the petrous portion of the facial nerve. Patients may also present with delayed-onset facial nerve palsy. Again, steroids are employed and surgery is considered, with mixed results.

Translation

Mental Disorders: Introduction

Mental disorders are common in medical practice and may present either as a primary disorder or as a comorbid condition. The prevalence of mental or substance use disorders in the United States is approximately 30%, only one-third of whom are currently receiving treatment. Global burden of disease statistics indicate that 4 of the 10 most important causes of disease worldwide are psychiatric in origin.

The revised fourth edition for use by primary care physicians of the *Diagnostic and Statistical Manual* (DSM-IV-PC) provides a useful synopsis of mental disorders most likely to be seen in primary care practice. The current system of classification is multiaxial and includes the presence or absence of a major mental disorder (axis I), any underlying personality disorder (axis II), general medical condition (axis III), psychosocial and environmental problems (axis IV), and overall rating of general psychosocial functioning (axis V).

Changes in health care delivery underscore the need for primary care physicians to assume responsibility for the initial diagnosis and treatment of the most common mental disorders. Prompt diagnosis is essential to ensure that patients have access to appropriate medical services and to maximize the clinical outcome. Validated patient-based questionnaires have been developed that systematically probe for signs and symptoms associated with the most prevalent psychiatric diagnoses and guide the clinician into targeted assessment. Prime MD (and a self-report form, the PHQ) and the Symptom-Driven Diagnostic System for Primary Care (SDDS-PC) are inventories that require only 10 minutes to complete and link patient responses to the formal diagnostic criteria of anxiety, mood, somatoform, and eating disorders and to alcohol abuse or dependence.

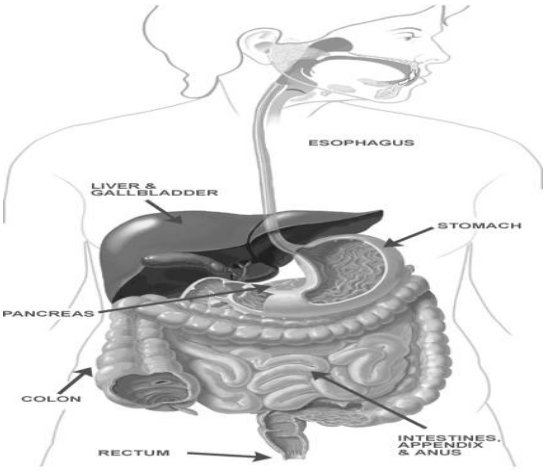
A physician who refers patients to a psychiatrist should know not only when doing so is appropriate but also how to refer, since societal misconceptions and the stigma of mental illness impede the process. Primary care physicians should base referrals to a psychiatrist on the presence of signs and symptoms of a mental disorder and not simply on the absence of a physical explanation for a patient's complaint.

Unit 10: Evaluation of the Patient with Gastrointestinal Disease

Reading 1

Evaluation of the patient with GI disease begins with a careful history and examination. Subsequent investigation with a variety of tools designed to test gut structure or function are indicated in selected cases. Some patients exhibit normal findings on diagnostic testing. In these individuals, validated symptom profiles are employed to confidently diagnose a functional bowel disorder.

The history of the patient with suspected GI disease has several components. Symptom timing suggests specific etiologies. Symptoms of short duration commonly result from acute infection, toxin exposure, or abrupt inflammation or ischemia. Long-standing symptoms point to underlying chronic inflammatory or neoplastic conditions or functional bowel disorders. Symptoms from mechanical obstruction, ischemia, inflammatory bowel disease, and functional bowel disorders are worsened by meals. Conversely, ulcer symptoms may be relieved by eating or antacids. Symptom patterns and duration may suggest underlying etiologies. Ulcer pain occurs at intermittent intervals lasting weeks to months, while biliary colic has a sudden onset and lasts up to several hours. Pain from acute inflammation as with acute pancreatitis is severe and persists for days to weeks. Meals elicit diarrhea in some cases of inflammatory bowel disease and irritable bowel syndrome. Defecation relieves discomfort in inflammatory bowel disease and irritable bowel syndrome. Functional bowel disorders are exacerbated by stress. Sudden awakening from sound sleep suggests organic rather than functional disease. Diarrhea from malabsorption usually improves with fasting, while secretory diarrhea persists without oral intake.



Symptom relation to other factors narrows the list of diagnostic possibilities. Obstructive symptoms with prior abdominal surgery raise concern for adhesions, whereas loose stools after gastrectomy or gallbladder excision suggest dumping syndrome or postcholecystectomy diarrhea. Symptom onset after travel prompts a search for enteric infection. Medications may produce pain, altered bowel habits, or GI bleeding. Lower GI bleeding likely results from neoplasms, diverticula, or vascular lesions in an older person and from anorectal abnormalities or inflammatory bowel disease in a younger individual. Celiac disease is prevalent in people of northern European descent, while inflammatory bowel disease is more common in certain Jewish populations. A sexual history may raise concern for sexually transmitted diseases or immunodeficiency.

For more than two decades, working groups have been convened to devise symptom criteria to improve the confident diagnosis of functional bowel disorders and to minimize the numbers of unnecessary diagnostic tests performed. The most widely accepted symptom-based criteria are the Rome criteria. When tested against findings of structural investigations, the Rome criteria exhibit

diagnostic specificities exceeding 90% for many of the functional bowel disorders.

Physical Examination

The physical exam complements information from the history. Abnormal vital signs provide diagnostic clues and determine the need for acute intervention. Fever suggests inflammation or neoplasm. Orthostasis is found with significant blood loss, dehydration, sepsis, or autonomic neuropathy. Skin, eye, or joint findings may point to specific diagnoses. Neck exam with swallowing assessment evaluates dysphagia. Cardiopulmonary disease may present with abdominal pain or nausea, thus lung and cardiac exams are important. Pelvic examination tests for a gynecologic source of abdominal pain. Rectal exam may detect blood, indicating gut mucosal injury or neoplasm or a palpable inflammatory mass in appendicitis. Metabolic conditions and gut motor disorders have associated peripheral neuropathy.

Inspection of the abdomen may reveal distention from obstruction, tumor, or ascites or vascular abnormalities with liver disease. Ecchymoses develop with severe pancreatitis. Auscultation can detect bruits or friction rubs from vascular disease or hepatic tumors. Loss of bowel sounds signifies ileus, while high-pitched, hyperactive sounds characterize intestinal obstruction. Percussion assesses liver size and can detect shifting dullness from ascites. Palpation assesses for hepatosplenomegaly as well as neoplastic or inflammatory masses. Abdominal exam is helpful in evaluating unexplained pain. Intestinal ischemia elicits severe pain but little tenderness. Patients with visceral pain may exhibit generalized discomfort, while those with parietal pain or peritonitis have directed pain, often with involuntary guarding, rigidity, or rebound. Patients with musculoskeletal abdominal wall pain may note tenderness exacerbated by Valsalva or straight-leg lift maneuvers.

Tools for Patient Evaluation

Laboratory, radiographic, and functional tests can assist in diagnosis of suspected GI disease. The GI tract also is amenable to internal evaluation with upper and lower endoscopy and to examination of luminal contents. Histopathologic exams of GI tissues complement these tests.

Reading 2

Selected laboratory tests facilitate the diagnosis of GI disease. Iron-deficiency anemia suggests mucosal blood loss, while vitamin B12 deficiency results from small-intestinal, gastric, or pancreatic disease. Either also can result from inadequate oral intake. Leukocytosis and increased sedimentation rates and C-reactive proteins are found in inflammatory conditions, while leukopenia is seen in viremic illness. Severe vomiting or diarrhea elicits electrolyte disturbances, acid-base abnormalities, and elevated blood urea nitrogen. Pancreaticobiliary or liver disease is suggested by elevated pancreatic or liver chemistries. Thyroid chemistries, cortisol, and calcium levels are obtained to exclude endocrinologic causes of GI symptoms. Pregnancy testing is considered for women with unexplained nausea. Serologic tests can screen for celiac disease, inflammatory bowel disease, rheumatologic diseases like lupus or scleroderma, and paraneoplastic dysmotility syndromes. Hormone levels are obtained for suspected endocrine neoplasia. Intraabdominal malignancies produce other tumor markers including the carcinoembryonic antigen CA 19-9 and -fetoprotein. Blood testing also monitors medication therapy in some diseases, as with thiopurine metabolite levels in inflammatory bowel disease. Other body fluids are sampled under certain

circumstances. Ascitic fluid is analyzed for infection, malignancy, or findings of portal hypertension. Cerebrospinal fluid is obtained for suspected central nervous system causes of vomiting. Urine samples screen for carcinoid, porphyria, and heavy metal intoxication.

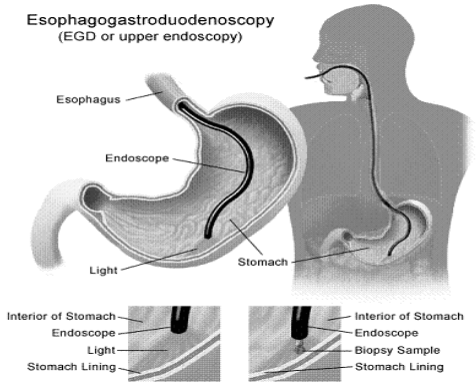
Translation

Luminal Contents

Luminal contents can be examined for diagnostic clues. Stool samples are cultured for bacterial pathogens, examined for leukocytes and parasites, or tested for *Giardia* antigen. Duodenal aspirates can be examined for parasites or cultured for bacterial overgrowth. Fecal fat is quantified in possible malabsorption. Stool electrolytes can be measured in diarrheal conditions. Laxative screens are done when laxative abuse is suspected. Gastric acid is quantified to rule out Zollinger-Ellison syndrome. Esophageal pH testing is done for refractory symptoms of acid reflux, whereas impedance techniques assess for nonacidic reflux. Pancreatic juice is analyzed for enzyme or bicarbonate content to exclude pancreatic exocrine insufficiency.

Endoscopy

The gut is accessible with endoscopy, which can provide the diagnosis of the causes of bleeding, pain, nausea and vomiting, weight loss, altered bowel function, and fever. lists the most common indications for the major endoscopic procedures. Upper endoscopy evaluates the esophagus, stomach, and duodenum, while colonoscopy assesses the colon and distal ileum.



Upper endoscopy is advocated as the initial structural test performed in patients with suspected ulcer disease, esophagitis, neoplasm, malabsorption, and Barrett's metaplasia because of its ability to directly visualize as well as biopsy the abnormality. Colonoscopy is the procedure of choice for colon cancer screening and surveillance as well as diagnosis of colitis secondary to infection, ischemia, radiation, and inflammatory bowel disease. Sigmoidoscopy examines the colon up to the splenic flexure and is currently used to exclude distal colonic inflammation or obstruction in young patients not at significant risk for colon cancer. For elusive GI bleeding secondary to arteriovenous malformations or superficial ulcers, small-intestinal examination is performed with push enteroscopy, capsule endoscopy, or double-balloon enteroscopy. Capsule endoscopy also can visualize small-intestinal Crohn's disease in individuals with negative barium radiography. Endoscopic retrograde cholangiopancreaticography (ERCP) provides diagnoses of pancreatic and biliary disease. Endoscopic ultrasound is useful for evaluating extent of disease in GI malignancy as well as exclusion of choledocholithiasis, evaluation of pancreatitis, drainage of pancreatic pseudocysts, and assessment of anal continuity.

Unit 11: Esophageal Structure and Function

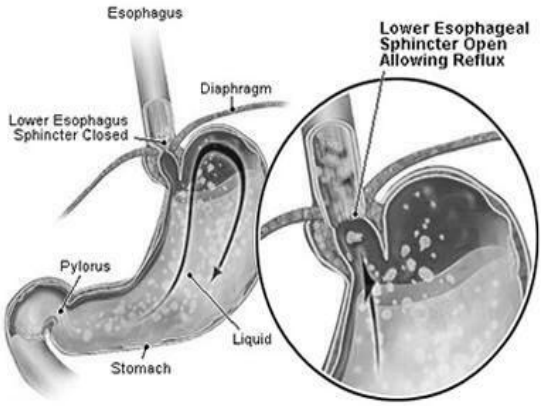
Reading 1

The esophagus is a hollow muscular tube coursing through the posterior mediastinum joining the hypopharynx to the stomach with a sphincter at each end. It functions to transport food and fluid between these ends, otherwise remaining empty. The physiology of swallowing, esophageal motility, and oral and pharyngeal dysphagia are described in **Chap. 38**. Esophageal diseases can be manifested by impaired function or pain. Key functional impairments are swallowing disorders and excessive gastroesophageal reflux. Pain, sometimes indistinguishable from cardiac chest pain, can result from inflammation, infection, dysmotility, or neoplasm.

Symptoms of Esophageal Disease

The clinical history remains central to the evaluation of esophageal symptoms. A thoughtfully obtained history will often expedite management. Important details include weight gain or loss, gastrointestinal bleeding, dietary habits including the timing of meals, smoking, and alcohol consumption. The major esophageal symptoms are heartburn, regurgitation, chest pain, dysphagia, odynophagia, and globus sensation.

Heartburn (pyrosis), the most common esophageal symptom, is characterized by a discomfort or burning sensation behind the sternum that arises from the epigastrium and may radiate toward the neck. Heartburn is an intermittent symptom, most commonly experienced after eating, during exercise, and while lying recumbent. The discomfort is relieved with drinking water or antacid but can occur frequently and interfere with normal activities including sleep. The association between heartburn and gastroesophageal reflux disease (GERD) is so strong that empirical therapy for GERD has become accepted management. However, the term "heartburn" is often misused and/or referred to with other terms such as "indigestion" or "repeating," making it important to clarify the intended meaning.

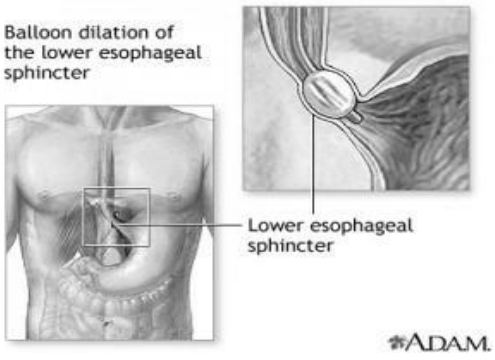


Regurgitation is the effortless return of food or fluid into the pharynx without nausea or retching. Patients report a sour or burning fluid in the throat or mouth that may also contain undigested food particles. Bending, belching, or maneuvers that increase intraabdominal pressure can provoke regurgitation. A clinician needs to discriminate among regurgitation, vomiting, and rumination. *Vomiting* is preceded by nausea and accompanied by retching. *Rumination* is a behavior in which recently swallowed food is regurgitated and then reswallowed repetitively for up to an hour. Although there is some linkage between rumination and mental deficiency, the behavior is also exhibited by unimpaired individuals who sometimes even find it pleasurable.

Chest pain is a common esophageal symptom with characteristics similar to cardiac pain, sometimes making this distinction difficult. Esophageal pain is usually experienced as a

pressure type sensation in the mid chest, radiating to the mid back, arms, or jaws. The similarity to cardiac pain is likely because the two organs share a nerve plexus and the nerve endings in the esophageal wall have poor discriminative ability among stimuli. Esophageal distention or even chemostimulation (e.g., with acid) will often be perceived as chest pain. Gastroesophageal reflux is the most common cause of esophageal chest pain.

Esophageal *dysphagia* is often described as a feeling of food "sticking" or even lodging in the chest. Important distinctions are between uniquely solid food dysphagia as opposed to liquid and solid, episodic versus constant dysphagia, and progressive versus static dysphagia. If the dysphagia is for liquids as well as solid food, it suggests a motility disorder such as achalasia. Conversely, uniquely solid food dysphagia is suggestive of a stricture, ring, or tumor. Of note, a patient's localization of food hang-up in the esophagus is notoriously imprecise. Approximately 30% of distal esophageal obstructions are perceived as cervical dysphagia. In such instances, the absence of concomitant symptoms generally associated with oropharyngeal dysphagia such as aspiration, nasopharyngeal regurgitation, cough, drooling, or obvious neuromuscular compromise should suggest an esophageal etiology.



Odynophagia is pain either caused by or exacerbated by swallowing. Odynophagia is more common with pill or infectious esophagitis than with reflux esophagitis and should prompt a search for these entities. When odynophagia does occur in GERD, it is likely related to an esophageal ulcer or deep erosion.

Globus sensation, alternatively labeled "globus hystericus," is the perception of a lump or fullness in the throat that is felt irrespective of swallowing. Although such patients are frequently referred for an evaluation of dysphagia, globus sensation is often relieved by the act of swallowing. As implied by its alternative name (globus hystericus), globus sensation often occurs in the setting of anxiety or obsessive-compulsive disorders. Clinical experience teaches that it is often attributable to GERD.

Water brash is excessive salivation resulting from a vagal reflex triggered by acidification of the esophageal mucosa. This is not a common symptom. Afflicted individuals will describe the unpleasant sensation of the mouth rapidly filling with salty thin fluid, often in the setting of concomitant heartburn.

Reading 2

Diagnostic Studies

Endoscopy

Endoscopy, also known as esophagogastroduodenoscopy (EGD) is the best test for the evaluation of the proximal gastrointestinal tract. Modern instruments produce high-quality color images of the esophageal, gastric, and duodenal lumen. Endoscopes also have an instrumentation channel through which biopsy forceps, sclerotherapy catheters, balloon dilators, or cautery devices can be utilized. The key advantages of endoscopy over barium radiography are: (1) increased sensitivity for the detection of mucosal lesions, (2) vastly increased sensitivity for the detection of abnormalities mainly identifiable by an abnormal color such as Barrett's metaplasia, (3) the ability to obtain biopsy specimens for histologic examination of suspected abnormalities, and (4) the

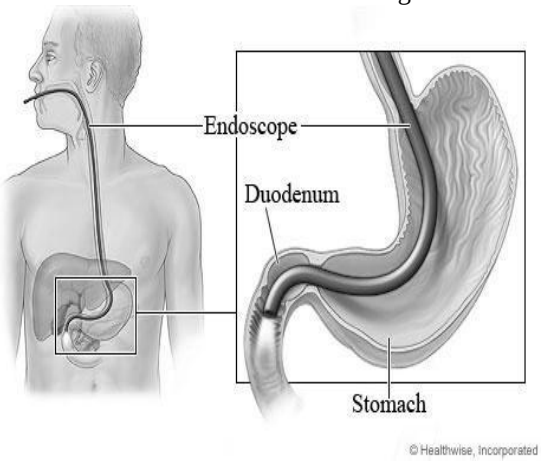
ability to dilate strictures during the examination. The main disadvantage of endoscopy is that it usually necessitates the use of conscious sedation with medicines such as midazolam (Versed), meperidine (Demerol), or fentanyl.

Radiography

Contrast radiography of the esophagus, stomach, and duodenum can demonstrate barium reflux, hiatal hernia, mucosal granularity, erosions, ulcerations, and strictures. The sensitivity of radiography compared with endoscopy for detecting esophagitis reportedly ranges from 22–95%, with higher grades of esophagitis (i.e., ulceration or stricture) exhibiting greater detection rates. Conversely, the sensitivity of barium radiography for detecting esophageal strictures is greater than that of endoscopy, especially when the study is done in conjunction with barium-soaked bread or a 13-mm barium tablet. Barium studies also provide an assessment of esophageal function and morphology that may be undetected on endoscopy. Hypopharyngeal pathology and disorders of the cricopharyngeal muscle are better appreciated on radiographic examination, particularly with videofluoroscopic recording. The major shortcoming of barium radiography is that it rarely obviates the need for endoscopy. Either a positive or a negative study is usually followed by an endoscopic evaluation either to clarify findings in the case of a positive examination or to add a level of certainty in the case of a negative one.

Endoscopic Ultrasound

Endoscopic ultrasound (EUS) instruments combine an endoscope with an ultrasound transducer to create a transmural image of the tissue surrounding the endoscope tip. The key advantage of EUS over alternative radiologic imaging techniques is much greater resolution attributable to the proximity of the ultrasound transducer to the area being examined.



Available devices can provide either radial imaging (360-degree, cross-sectional) or a curved linear image that can guide fine-needle aspiration of imaged structures such as lymph nodes or tumors. Major esophageal applications of EUS are to stage esophageal cancer, to evaluate dysplasia in Barrett's esophagus, and to assess submucosal tumors.

Translation

Esophageal Manometry

Esophageal manometry, or motility testing, entails positioning a pressure sensing catheter within the esophagus and then observing the contractility following test swallows. The upper and lower esophageal sphincters appear as zones of high pressure that relax on swallowing while the intersphincteric esophagus exhibits peristaltic contractions. Manometry is used to diagnose motility disorders (achalasia, diffuse esophageal spasm) and to assess peristaltic integrity prior to the surgery for reflux disease. Technological advances have rebranded esophageal manometry as high-resolution esophageal pressure topography. Manometry can also be combined with intraluminal impedance monitoring. Impedance recordings utilize a catheter with a series of paired electrodes. Esophageal luminal contents in contact with the electrodes decrease (liquid) or increase (air) the impedance signal allowing detection of anterograde or retrograde transit of esophageal bolus transit.

Reflux Testing

GERD is often diagnosed in the absence of endoscopic esophagitis, which would otherwise define the disease. This occurs in the settings of partially treated disease, an abnormally sensitive esophageal mucosa, or without obvious explanation. In such instances, reflux testing can demonstrate excessive esophageal exposure to refluxed gastric juice, the physiologic abnormality of GERD. This can be done by ambulatory 24- to 48-hour esophageal pH recording using either a wireless pH-sensitive transmitter that is anchored to the esophageal mucosa or with a transnasally positioned wire electrode with the tip stationed in the distal esophagus. Either way, the outcome is expressed as the percentage of the day that the pH was less than 4 (indicative of recent acid reflux), with values exceeding 5% indicative of GERD.

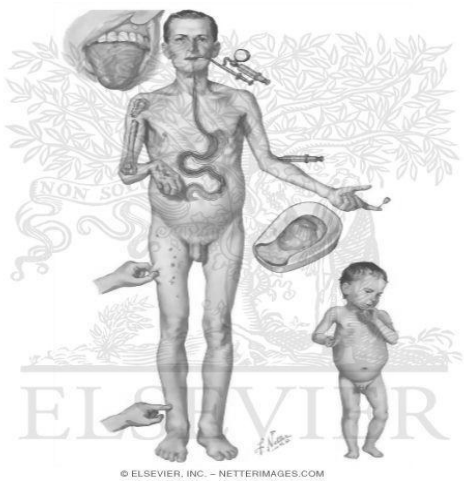
Reflux testing is useful with atypical symptoms or an inexplicably poor response to therapy. Intraluminal impedance monitoring can be added to pH monitoring to detect reflux events irrespective of whether or not they are acidic, potentially increasing the sensitivity of the study.

Unit 12: Disorders of Absorption

Reading 1

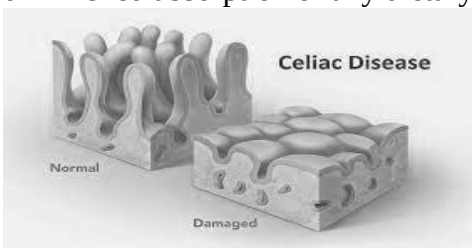
Introduction

Disorders of absorption constitute a broad spectrum of conditions with multiple etiologies and varied clinical manifestations. Almost all of these clinical problems are associated with *diminished* intestinal absorption of one or more dietary nutrients and are often referred to as the *malabsorption syndrome.* This term is not ideal as it represents a pathophysiologic state, does *not* provide an etiologic explanation for the underlying problem, and should not be considered an adequate final diagnosis. The only clinical situations in which absorption is *increased* are hemochromatosis and Wilson's disease, in which absorption of iron and copper, respectively, are increased.



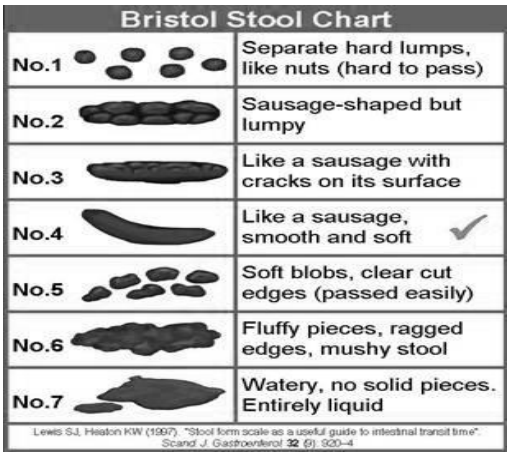
Most, but not all, malabsorption syndromes are associated with *steatorrhea,* an increase in stool fat excretion of >6% of dietary fat intake. Some malabsorption disorders are not associated with steatorrhea: primary lactase deficiency, a congenital absence of the small intestinal brush border disaccharidase enzyme lactase, is associated with lactose "malabsorption," and pernicious anemia is associated with a marked decrease in intestinal absorption of cobalamin (vitamin B12) due to an absence of gastric parietal cell intrinsic factor required for cobalamin absorption.

Disorders of absorption must be included in the differential diagnosis of diarrhea. First, diarrhea is frequently associated with and/or is a consequence of the diminished absorption of one or more dietary nutrients. The diarrhea may be secondary either to the intestinal process that is responsible for the steatorrhea or to steatorrhea per se. Thus, celiac disease (see below) is associated with both extensive morphologic changes in the small intestinal mucosa and reduced absorption of several dietary nutrients; in contrast, the diarrhea of steatorrhea is the result of the effect of nonabsorbed dietary fatty acids on intestinal, usually colonic, ion transport. For example, oleic acid and ricinoleic acid (a bacterially hydroxylated fatty acid that is also the active ingredient in castor oil, a widely used laxative) induce active colonic Cl ion secretion, most likely secondary to increasing intracellular Ca. In addition, diarrhea per se may result in mild steatorrhea (<11 g fat excretion while on a 100-g fat diet). Second, most patients will indicate that they have diarrhea, not that they have fat malabsorption. Third, many intestinal disorders that have diarrhea as a prominent symptom (e.g., ulcerative colitis, traveler's diarrhea secondary to an enterotoxin produced by *Escherichia coli*) do not necessarily have diminished absorption of any dietary nutrient.



Diarrhea as a *symptom* (i.e., when used by patients to describe their bowel movement

pattern) may be a decrease in stool consistency, an increase in stool volume, an increase in number of bowel movements, or any combination of these three changes. In contrast, diarrhea as a *sign* is a quantitative increase in stool water or weight of >200–225 mL or gram per 24 h, when a Western-type diet is consumed. Individuals consuming a diet with higher fiber content may normally have a stool weight of up to 400 g/24 h. Thus, the clinician must clarify what an individual patient means by diarrhea. Some 10% of patients referred to gastroenterologists for further evaluation of unexplained diarrhea do not have an increase in stool water when it is determined quantitatively. Such patients may have small, frequent, somewhat loose bowel movements with stool urgency that is indicative of proctitis but do not have an increase in stool weight or volume.



It is also critical to establish whether a patient's diarrhea is secondary to diminished absorption of one or more dietary nutrients, in contrast to diarrhea that is due to small- and/or large-intestinal fluid and electrolyte secretion. The former has often been termed *osmotic diarrhea*, while the latter has been referred to as *secretory diarrhea*. Unfortunately, both secretory and osmotic elements can be present simultaneously in the same disorder; thus, this separation is not always precise. Nonetheless, two studies—determination of stool electrolytes and observation of the effect of a fast on stool output—can help make this distinction.

The demonstration of the effect of prolonged (>24 h) fasting on stool output can be very effective in suggesting that a *dietary nutrient* is responsible for the individual's diarrhea. A secretory diarrhea associated with enterotoxin-induced traveler's diarrhea would not be affected by prolonged fasting, as enterotoxin-induced stimulation of intestinal fluid and electrolyte secretion is not altered by eating. In contrast, diarrhea secondary to lactose malabsorption in primary lactase deficiency would undoubtedly cease during a prolonged fast. Thus, a substantial decrease in stool output while fasting during a quantitative stool collection of at least 24 h is presumptive evidence that the diarrhea is related to malabsorption of a dietary nutrient. The persistence of stool output while fasting indicates that the diarrhea is likely secretory and that the cause of diarrhea is *not* a dietary nutrient. Either a luminal (e.g., *E. coli* enterotoxin) or circulating (e.g., vasoactive intestinal peptide) secretagogue could be responsible for the patient's diarrhea persisting unaltered during a prolonged fast. The observed effects of fasting can be compared and correlated with stool electrolyte and osmolality determinations.

Measurement of stool electrolytes and osmolality requires the comparison of stool Na^+ and K^+ concentrations determined in liquid stool to the stool osmolality to determine the presence or absence of a so-called stool osmotic gap. The following formula is used: $2 \times (\text{stool } [Na^+] + \text{stool } [K^+])$ stool osmolality

Reading 2

Nutrient Digestion and Absorption

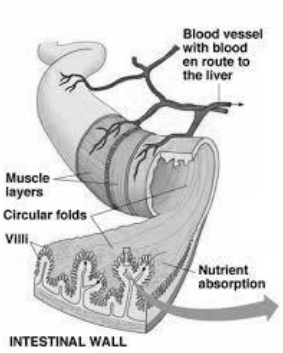
The lengths of the small intestine and colon

are ~300 cm and ~80 cm, respectively. However, the effective functional surface area is approximately 600-fold greater than that of a hollow tube as a result of the presence of folds, villi (in the small intestine), and microvilli. The functional surface area of the small intestine is somewhat greater than that of a doubles tennis court. In addition to nutrient digestion and absorption, the intestinal epithelia have several other functions:

Barrier and immune defense. The intestine is exposed to a large number of potential antigens and enteric and invasive microorganisms, and it is extremely effective preventing the entry of almost all these agents. The intestinal mucosa also synthesizes and secretes secretory IgA.

Fluid and electrolyte absorption and secretion. The intestine absorbs ~7–8 L of fluid daily, comprising dietary fluid intake (1–2 L/d) and salivary, gastric, pancreatic, biliary, and intestinal fluid (6–7 L/d). Several stimuli, especially bacteria and bacterial enterotoxins, induce fluid and electrolyte secretion that may lead to diarrhea (Chap. 128).

Synthesis and secretion of several proteins. The intestinal mucosa is a major site for the production of proteins, including apolipoproteins.



Production of several bioactive amines and peptides. The intestine is one of the largest endocrine organs in the body and produces several amines (e.g., 5-hydroxytryptophan) and peptides that serve as paracrine and hormonal mediators of intestinal function.

Translation

The small and large intestines are distinct anatomically (villi are present in the small intestine but are absent in the colon) and functionally (nutrient digestion and absorption take place in the small intestine but not in the colon). No precise anatomic characteristics separate duodenum, jejunum, and ileum, although certain nutrients are absorbed exclusively in specific areas of the small intestine. However, villous cells in the small intestine (and surface epithelial cells in the colon) and crypt cells have distinct anatomic and functional characteristics. Intestinal epithelial cells are continuously renewed, with new proliferating epithelial cells at the base of the crypt migrating over 48–72 h to the tip of the villus (or surface of the colon), where they are well-developed epithelial cells with digestive and absorptive function. This high rate of cell turnover explains the relatively rapid resolution of diarrhea and other digestive tract side effects during chemotherapy as new cells not exposed to these toxic agents are produced. Equally important is the paradigm of separation of villous/surface cell and crypt cell function: Digestive hydrolytic enzymes are present primarily in the brush border of villous epithelial cells. Absorptive and secretory functions are also separated, with villous/surface cells primarily, but not exclusively, being the site for absorptive function, while secretory function is present in crypts of both the small and large intestine.

Nutrients, minerals, and vitamins are absorbed by one or more active transport mechanisms. Active transport mechanisms are energy-dependent and mediated by membrane transport proteins. These processes will result in the net movement of a substance against or in the absence of an electrochemical concentration gradient. Intestinal absorption of amino acids and monosaccharides, e.g., glucose, is also a specialized form of active transport—secondary active transport. The movement of these actively transported nutrients against a concentration gradient is Na+-dependent and is due to a Na+ gradient across the apical membrane. The Na+ gradient is maintained by Na+, K+-adenosine triphosphatase (ATPase), the so-called Na+ pump located on the basolateral membrane, which extrudes Na+ and maintains low intracellular [Na] as well as the Na+ gradient across the apical membrane.

Unit 13: Liver

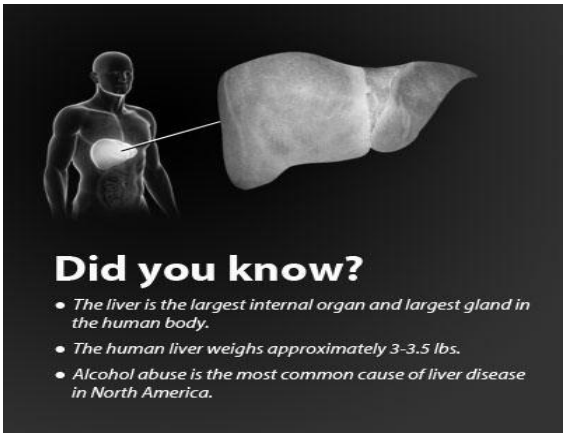
Reading 1

Anatomy

It is unclear if the ancient Greeks understood concepts like functional hepatic reserve and hepatic regeneration, but they may well have had some insight into the remarkable regenerative capacity of the liver based on the well-known myth of Prometheus. Zeus punished Prometheus for giving fire to humans. The eternal torment of Prometheus was to have his liver devoured daily by an apparently surgically adept eagle. His liver would regenerate completely over the next 24 hours, assuring a meal for the eagle the next day.

Around 2000 B.C. the Babylonians knew the liver had an impressive blood supply and capacity for hemorrhage, thus they considered it to be the seat of the soul. For many years, surgeons operated on the liver only with trepidation, often being confronted with persistent or massive hemorrhage. However, recent advances in knowledge of hepatobiliary anatomy and advances in techniques for major liver resections have produced marked reductions in the high morbidity and mortality rates classically associated with hepatobiliary operations.

The liver is the largest solid organ in the body, weighing about 1.5 kg in the adult. It lies in the right upper quadrant of the abdomen and is completely protected by the thoracic rib cage. Its normal expanse is from the nipple line at the fourth intercostal space down to the costal margin in the midclavicular line. It is completely surrounded by a peritoneal membrane, known as Glisson's capsule. The cephalad aspect of the liver is in contact with the left and right hemidiaphragm, while the caudal surface is in contact with the stomach, duodenum, and colon. Glisson's capsule also envelops the portal triad structures as they enter the liver. The posterior aspect of the liver is in contact with the right kidney and adrenal gland.

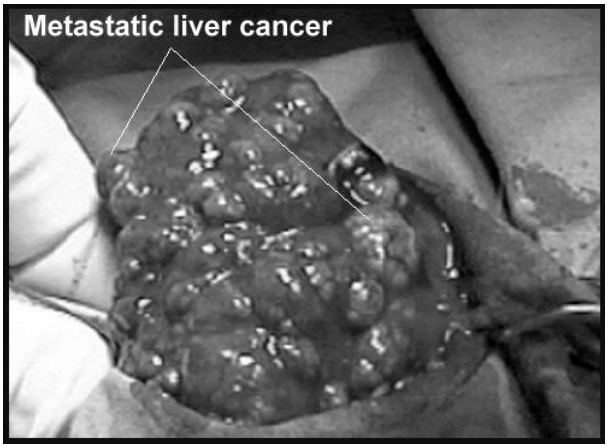


Malignant Liver Tumors

Surgical Treatment

The first recorded successful elective resection of a liver tumor in the United States was performed by Tiffany in 1890, followed in 1891 by Lucke in Europe. If they were not already aware of the risk of massive hemorrhage from the liver, surgeons were reminded of it by Elliot in 1897 in his report of an attempted resection of a liver tumor, when he stated that the liver "is so friable, so full of gaping vessels and so evidently incapable of being sutured that it seemed impossible to successfully manage large wounds of its substance." Most surgeons continued to choose judiciously which patients

they would consider for an elective liver resection, if any, until a greater understanding of hepatobiliary anatomy was published by Couinaud in 1954. Couinaud's description of the segmental liver anatomy based on portal venous inflow and hepatic venous outflow, and the identification of eight hepatic segments (numbered I through VIII) were key steps in the development of safe, anatomic hepatic resections.



Building on the anatomic and surgical foundation laid down by investigators 50 to 100 years ago, modern surgeons are performing elective operations for liver tumors with increasing frequency. The persistent interest in improved and safer surgical treatments for malignant liver tumors is based on the fact that surgical extirpation or complete cytodestruction currently provides patients with the best chance for long-term disease-free and overall survival. This is true for disease confined to the liver, whether treating patients with primary or metastatic liver cancers.

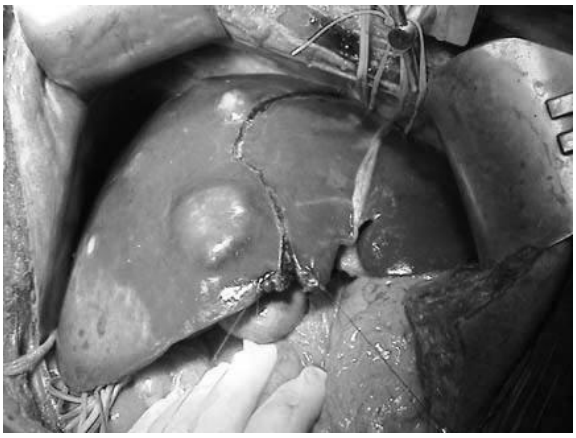
Improved preoperative imaging studies, routine use of intraoperative ultrasonography, understanding of the vascular and segmental anatomy of the liver, application of new surgical instruments and technology, and improved perioperative anesthesia management have combined to increase the number of patients undergoing successful hepatic resections as treatment for primary or metastatic liver tumors. HCC is one of the most common solid human cancers, with an annual incidence estimated to be approximately 1 million new patients. In addition to being a common site for the development of primary malignancy, the liver is second only to lymph nodes as a common site of metastasis from other solid cancers. 118 It is not uncommon, particularly in patients with colorectal adenocarcinoma, for the liver to be the only site of metastatic disease. Surgical resection of HCC, colorectal cancer hepatic metastases, and carefully selected patients with liver-only metastases from other types of primary tumors can result in significant long-term survival benefit in 20 to 45% of patients.

Indications for Resection

The important role of liver resection as a treatment for colorectal cancer metastases was solidified by the report in 1988 from the Registry of Hepatic Metastases. 121 This retrospective chart review from 24 institutions identified 859 patients who underwent resection of colorectal liver metastases between 1948 and 1985. The 5-year actuarial survival rate in these patients was 33%, with a 5-year actuarial disease-free survival rate of 21%. Several indicators of poor prognosis also were established by a subset analysis, including a 0% 5-year survival rate when extrahepatic metastatic disease was present, a significantly reduced survival rate if the tumor-free resection margin was less than 1 cm or if the primary tumor was stage III (node positive) versus stage II (node negative), and reduced 5-year overall and disease-free survival rates in patients who underwent resection of three or more metastases. The authors noted that patients with three metastases had a significantly poorer disease-free survival rate than those with a single

metastasis or two metastases, and that patients with four or more metastases appeared to do at least as poorly. Based on those observations, the presence of four or more liver metastases from colorectal cancer became a contraindication to resection, even when technically feasible with an adequate remaining volume of perfused hepatic parenchyma.

The Registry of Hepatic Metastases report is a retrospective review of patients who underwent operation largely before the availability of adequate preoperative and intraoperative imaging modalities. Furthermore, careful pathologic analysis and an accurate count of the number of lesions were not available in all of the patients. Most of the patients were identified by the development of symptoms, abnormalities in serum liver tests, or an elevated serum tumor marker in the later period of the study. The study included 509 (59%) patients with a solitary liver metastasis, indicating that this was a highly selected group of patients. Of the 149 patients who had three or more metastases, a breakdown of survival by number of metastases was not provided, and the actuarial 5-year survival rate for this group was 18%.



Recent re-evaluations of the number of metastases that should be considered for resection have demonstrated that there is a potential survival benefit in patients with four or more metastases. In contrast to the registry data, all patients in these modern series underwent thorough intraoperative ultrasonography to detect metastatic foci within the liver not identified by preoperative imaging studies, as well as to ensure that the resection be performed with a high probability of tumor-free margins. A study of 235 patients from Japan who underwent hepatic resection for metastatic colorectal cancer included 53 patients (22.6%) who had more than four metastases, including some patients with as many as 10 to 15 lesions. The actuarial 10-year life expectancy of patients with four or more lesions was 29%, which was almost equivalent to the long-term survival of patients who underwent resection of a solitary metastasis. Patients with two or three metastases actually had a slightly worse long-term survival than patients with more than four tumors. A study from the United States of 155 patients who underwent resection of more than four colorectal liver metastases revealed an overall 5-year survival rate of 23%. As the number of resected metastases increased above nine, there was a significant reduction in long-term survival probability. On multivariate analysis, only positive resection margins and a large number of metastases were significant prognostic indicators for poor outcome.

The indications for resection of HCC also have been re-evaluated. Studies from the 1980s and early 1990s suggested that the presence of cirrhosis or multiple tumors were harbingers of poor outcome after resection of HCC. 109 However, these studies were performed during a time when operative mortality rates in cirrhotic HCC patients ranged from 6 to 15%, and the need for intraoperative and postoperative blood transfusion was common. Improved outcomes have been demonstrated in more recent studies in which modern hepatic resection techniques

were employed. Specifically, perioperative blood transfusion rates fell from 69 to 87% in the earlier time period to 23 to 39% in more recent series. The operative and hospital death rate was reduced from 13.2% to under 2%, and 5-year survival rates improved from 19 to 32% to 25 to 49%, despite all patients harboring pathologically proven cirrhosis.

Reading 2

Laparoscopic Hepatic Resection

Laparoscopy has a definite role in the diagnosis and staging of patients with gastrointestinal malignancies. A therapeutic role for laparoscopic liver resection has yet to be established.

The development of endoscopic vascular staplers and the harmonic scalpel have increased interest in laparoscopic approaches to benign and malignant liver tumors, although minimally invasive liver resection has not advanced as far as laparoscopic colon, adrenal, and spleen resection. Over the last several years, small series of patients treated with laparoscopic liver resection have been reported. The large majority of liver resection cases completed laparoscopically have been left lateral segmentectomies, segmental or partial segmental resections, or wedge resections. 128,129 Laparoscopic ultrasonography is performed to localize tumors and to mark the surface of the liver with electrocautery to ensure an adequate margin-negative resection. The parenchyma can be transected using endovascular staplers, the harmonic scalpel, or with finger fracture through a hand port using a pneumosleeve. The reasons for converting a laparoscopic to an open liver resection include dense adhesions that preclude adequate laparoscopic visualization, inadequate tumor-free margins, or brisk hemorrhage during laparoscopic resection.

Liver diseases

There are many kinds of liver diseases. Viruses cause some of them, like hepatitis A, hepatitis B and hepatitis C. Others can be the result of drugs, poisons or drinking too much alcohol. If the liver forms scar tissue because of an illness, it's called cirrhosis. Jaundice, or yellowing of the skin, can be one sign of liver disease. Cancer can affect the liver. You could also inherit a liver disease such as hemochromatosis

Hepatitis A: Our liver is the largest organ inside your body. It helps your body digest food, store energy, and remove poisons. Hepatitis is an inflammation of the liver. One type, hepatitis A, is caused by the hepatitis A virus (HAV). The disease spreads through contact with an infected person's stool. You can get it from

- Eating food made by an infected person who did not wash their hands after using the bathroom
- Drinking untreated water or eating food washed in untreated water
- Putting into your mouth a finger or object that came into contact with an infected person's stool
- Having close contact with an infected person, such as through sex or caring for someone who is ill

Most people do not have any symptoms. If you do have symptoms, you may feel as if you have the flu. You may also have yellowish eyes and skin, called jaundice. A blood test will show if you have HAV.

HAV usually gets better in a few weeks without treatment. However, some people can have symptoms for up to 6 months. Your doctor may suggest medicines to help relieve your symptoms.

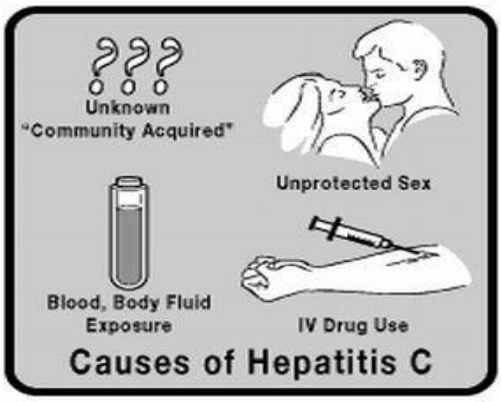
The hepatitis A vaccine can prevent HAV. Good hygiene can also help. Wash your hands thoroughly before preparing food, after using the toilet, or after changing a diaper. International travelers should be careful about drinking tap water.

Hepatitis B: Hepatitis is an inflammation of the liver. One type, hepatitis B, is caused by the hepatitis B virus (HBV). Hepatitis B spreads by contact with an infected person's blood, semen, or other body fluid. An infected woman can give hepatitis B to her baby at birth.

If you get HBV, you may feel as if you have the flu. You may also have jaundice, a yellowing of skin and eyes, dark-colored urine, and pale bowel movements. Some people have no symptoms at all. A blood test can tell if you have it. HBV usually gets better on its own after a few months. If it does not get better, it is called chronic HBV, which lasts a lifetime. Chronic HBV can lead to scarring of the liver, liver failure, or liver cancer.

There is a vaccine for HBV. It requires three shots. All babies should get the vaccine, but older children and adults can get it too. If you travel to countries where Hepatitis B is common, you should get the vaccine.

One type, hepatitis C, is caused by the hepatitis C virus (HCV). It usually spreads through contact with infected blood. It can also spread through sex with an infected person and from mother to baby during childbirth.



Most people who are infected with hepatitis C don't have any symptoms for years. If you do get symptoms, you may feel as if you have the flu. You may also have jaundice, a yellowing of skin and eyes, dark-colored urine, and pale bowel movements. A blood test can tell if you have it. Usually, hepatitis C does not get better by itself. The infection can last a lifetime and may lead to scarring of the liver orliver cancer. Medicines sometimes help, but side effects can be a problem. Serious cases may need a liver transplant. There is no vaccine for HCV.

Unit 14: Leishmaniasis

Reading 1

Leishmaniasis is a disease caused by an intracellular protozoan parasite (genus *Leishmania*) transmitted by the bite of a sandfly. The clinical spectrum of leishmaniasis ranges from a self-resolving cutaneous ulcer to a mutilating mucocutaneous disease and even to a lethal systemic illness. Therapy has long been a challenge in the more severe forms of the disease, and it is made more difficult by the emergence of drug resistance. With the exception of Australia, the Pacific Islands, and Antarctica, the parasites have been identified throughout large portions of the world.

The FDA has approved oral miltefosine (Impavido) for the treatment of visceral, cutaneous, and mucosal leishmaniasis in patients aged 12 years or older. Approval was based on 4 clinical studies, in a total of 730 patients. The drug's labeling will include a boxed warning against use of miltefosine during pregnancy because of a risk of fetal harm.

Although the *Leishmania* species differ clinically and biologically, their characteristics overlap and each clinical syndrome can be produced by multiple species of *Leishmania*.

Cutaneous Leishmaniasis

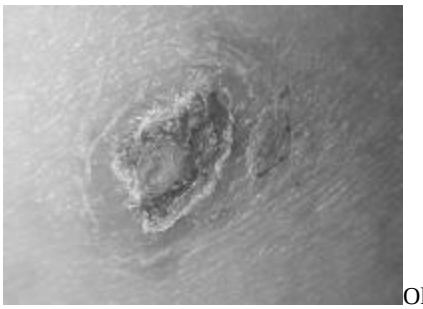
The broad spectrum of clinical manifestations of cutaneous leishmaniasis is often compared with that of leprosy. Cutaneous leishmaniasis can be simple or diffuse (disseminated). Different species, as well as host factors, can also affect the clinical picture, in which some species cause "wet" ulcers and others "dry" ulcers.

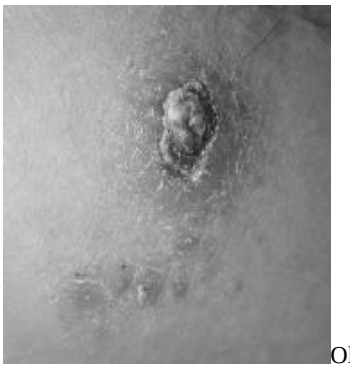
The hallmark of cutaneous leishmaniasis is skin lesions, which can spontaneously heal in 2-10 months. Inoculation occurs after a sandfly bites an exposed part of the body (usually the legs, arms, neck, or face). Incubation occurs over weeks to months, followed by the appearance of an erythematous papule, which can evolve into a plaque or ulcer. These lesions are usually painless.

No systemic symptoms are evident. After recovery or successful treatment, cutaneous leishmaniasis induces immunity to reinfection by the species of *Leishmania* that caused the disease.

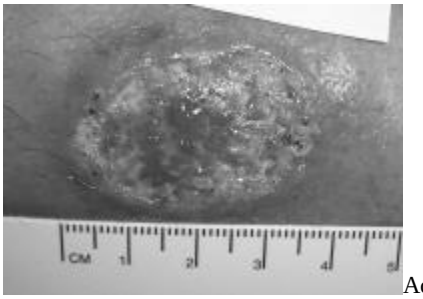
Localized cutaneous disease

Both New World and Old World species cause localized cutaneous leishmaniasis. New World disease usually presents with a solitary nodule, whereas Old World disease is associated with multiple lesions. Systemic symptoms are absent. Wound progression occurs over time and may exhibit localized lymphangitic spread. See the images below.


Old World localized cutaneous leishmaniasis located on the trunk of a soldier stationed in Kuwait. This lesion was a 3-cm by 4-cm nontender ulceration that developed over the course of 6 months at the site of a sandfly bite. The patient reported seeing several rats around his encampment.


Old World cutaneous leishmaniasis located on the right arm of the same soldier stationed in Kuwait. This 2-cm by 3-cm lesion was located at the exposed area where the sleeve ended. Note the satellite lesions.

The lesions are usually without pain or pruritus, although secondary bacterial infection may complicate the wound (see the following image). Healing may occur spontaneously over 2-12 months and is followed by scarring and changes in pigmentation. New World disease may progress to mucocutaneous leishmaniasis.

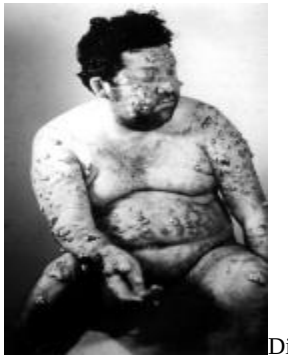

Active cutaneous leishmaniasis lesion with likely secondary infection in a soldier.

Diffuse Cutaneous Leishmaniasis

Diffuse cutaneous disease develops in an anergic host with poor immune response. This condition is associated with a deficient cell-mediated immunity that enables the parasite to disseminate in the subcutaneous tissues and has been reported in patients with human immunodeficiency virus (HIV) infection.

Infection is characterized by a primary lesion, which slowly spreads to involve multiple areas of the skin (face, ears, extremities, buttocks) until the whole body is affected. Plaques, ulcers, and nodules may form over the entire body, resembling lepromatous leprosy (see the image below). However, no neurologic or systemic invasion is involved; as a result, although the lesions are neither destructive nor erosive, they are disfiguring. The infections are chronic and may recur after treatment.

Although diffuse disease is more common with New World species in Central and South America, Old World *L aethiopica* may progress to diffuse disease in East Africa.

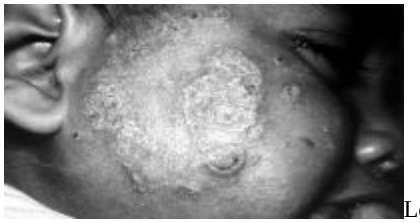

Diffuse (disseminated) cutaneous leishmaniasis. Courtesy of Jacinto Convit, National Institute of Dermatology in Caracas, Venezuela.

Reading 2

Leishmaniasis Recidivans

Leishmaniasis recidivans may occur years after a localized cutaneous lesion has healed, commonly presenting on the face (see the following image). New ulcers and papules

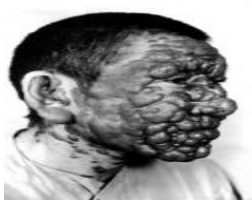
form over the edge of the old scar and proceed inward to form a psoriasiform lesion. Infection may be from reactivation of dormant parasites or new infection from a different species. Skin trauma can result in activation of seemingly latent cutaneous infection long after the initial bite. The infections tend to be resistant to treatment.


Leishmaniasis recidivans. Courtesy of Kenneth F. Wagner, MD.

Post-kala-azar dermal leishmaniasis

Post-kala-azar dermal leishmaniasis follows the treatment of visceral leishmaniasis and has predominantly been described in Africa (about 2% of cases) and India (about 10% of cases).

The Indian variant occurs in patients 1-2 years and as long as 20 years after recovery from visceral leishmaniasis. This condition is characterized by multiple, hypopigmented, erythematous macules. Over time, these macules can transform into large nontender plaques and nodules that involve the face and trunk (see the image below). The disease resembles lepromatous leprosy and requires intensive therapy. The African variant occurs shortly after treatment of visceral leishmaniasis and is characterized by an erythematous papular rash on the face, buttocks, and extremities. These lesions spontaneously resolve over the course of several months.


Post–kala-azar dermal leishmaniasis. Courtesy of R. E. Kuntz and R. H. Watten, Naval Medical Research Unit, Taipei, Taiwan.

In Sudan, patients often present with a facial rash consisting of small papules resembling measles that spreads to involve other parts of the body. This syndrome may heal spontaneously, but relapse is common. Established disease is generally difficult to treat.

Post–kala-azar dermal leishmaniasis that is resistant to antimonial agents has been reported, with an incidence rate of 1 in 700 cases.

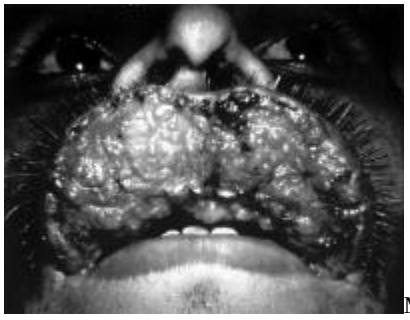
Mucocutaneous leishmaniasis

Mucocutaneous disease, also called *espundia* in South America, usually develop by metastasis from disseminated protozoa rather than by local spread. This condition is most commonly caused by New World species, although Old World *L aethiopica* has also been reported to cause this syndrome. Secondary infection plays a prominent role in the size and persistence of ulcers.

Infection by *L (Viannia) braziliensis* may lead to mucosal involvement in up to 10% of infections, depending on the region in which it was acquired. The incubation period is from 1 to 3 months. The initial infection is characterized by a persistent cutaneous lesion that eventually heals, although as many as 30% of patients report no prior evidence of leishmaniasis.

Ulcer progression is slow and steady. Several years late r, oral and respiratory mucosal involvement occurs, causing inflammation and mutilation of the nose, mouth, oropharynx,

and trachea (see the following image), resulting in symptoms of nasal obstruction and bleeding. These can become sites of infection, sometimes leading to sepsis. Cases in which the time between the primary lesion and the appearance of mucosal involvement is up to 2 decades have been reported.


Mucocutaneous leishmaniasis. Courtesy of Kenneth F. Wagner, MD.

Progressive mucocutaneous disease is difficult to treat and often recurs. With prolonged infection, death occurs from respiratory compromise and malnutrition. Mucocutaneous leishmaniasis may arise after inadequate treatment of certain*Leishmania* species. Children are rarely affected.

Translation

Visceral leishmaniasis

Visceral disease, the most devastating and fatal form of leishmaniasis, is classically known as kala-azar or the Indian name for “black fever/disease,” which is a reference to the characteristic darkening of the skin that is seen in patients with this condition. Other terms used to describe visceral disease include Dumdum fever, Assam fever, and infantile splenomegaly in various parts of the world.

This condition occurs with both New and Old World species and results from systemic infection of the liver, spleen, and bone marrow. The spectrum of illness ranges from asymptomatic infection or self-resolving disease to fulminant, severe, life-threatening infection; many subclinical cases occur and go unrecognized for each clinically recognized case.

The syndrome is characterized by the pentad of fever, weight loss, hepatosplenomegaly, pancytopenia, and hypergammaglobulinemia. The fever is continuous or remittent and becomes intermittent at a later stage. It is also characteristically described as a double rise in 24 hours, in which waves of pyrexia may be followed by a period without fever. Patients may also report night sweats, weakness, diarrhea, malaise, and anorexia. Melanocyte stimulation and xerosis can occur, causing characteristic skin hyperpigmentation.

Onset of visceral disease can be insidious or sudden. The incubation period varies after infection (usually 3-6 mo, but can be months or years) and may depend on the patient's age and immune status as well as the species of *Leishmania*. Young malnourished children are most susceptible to developing progressive infection; those who present later in the course of the disease may present with edema caused by hypoalbuminemia, hemorrhage caused by thrombocytopenia, or growth failure caused by features of chronic infection.

If visceral disease is left untreated, death frequently occurs within 2 years which may be due to hemorrhage (secondary to infiltration of the hematopoietic system), severe anemia, immunosuppression, and/or secondary infections.

A variant of visceral leishmaniasis has been described in US soldiers who participated in the Gulf War. This is associated with light parasitic burden and mild symptoms including fever, malaise, and nausea.

Viscerotropic leishmaniasis

Viscerotropic leishmaniasis has an indolent but distinct clinical presentation and does not appear to progress to full visceral leishmaniasis. Patients have presented with an array of symptoms months to years after infection, including fever, rigors, fatigue, malaise, nonproductive cough, intermittent diarrhea, headache, arthralgias, myalgias, nausea, adenopathy, transient hepatosplenomegaly, and abdominal pain.

Although *L tropica* traditionally has been associated with cutaneous leishmaniasis, several reports of visceral disease have been reported from Kenya, India, and Israel. In addition, reports of patients returning from the Middle East showed presentations ranged from 1 month to 2 years after exposure, with many of symptoms described above: malaise, fatigue, intermittent fever, cough, diarrhea, abdominal pain, and other gastrointestinal symptoms.

Unit 15: Orthopaedics

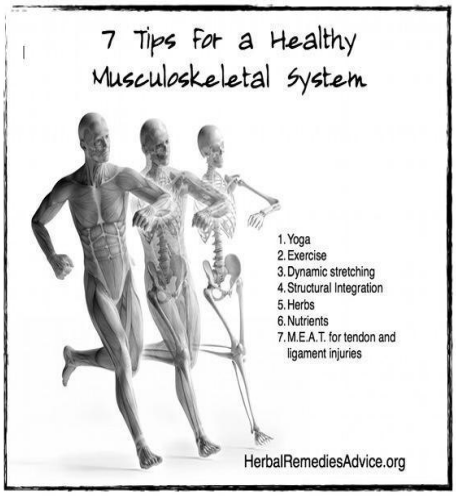
***from* Schwartz's Principles…**

Reading 1

Introduction

Nicolas Andry coined the word from which the English word orthopaedics is derived when he wrote a book titled *L'Orthopedie* in 1741. Orthopaedics is derived from the two Greek words Andry chose: *orthos*, meaning straight or free from deformity, and *pais*, meaning child. Since that time orthopaedics has expanded to include the evaluation and treatment of all musculoskeletal injury and disorders. Until the later half of the twentieth century, orthopaedics was predominately the nonoperative treatment of fractures, treatment of musculoskeletal infections (often tuberculosis), and polio. As we enter the twenty-first century, orthopaedic surgery includes the replacement of degenerated joints, operative fixation of fractures, arthroscopic repair of torn meniscus, rotator cuffs, and a whole host of other intra-articular abnormalities. Musculoskeletal research laboratories have found means of stimulating the body to make new bones and soon cartilage production will be accomplished. Gene therapies for a variety of musculoskeletal diseases are on the horizon. Orthopaedics is a dynamic field and orthopaedic surgeons treat both sexes and all ages of patients with a wide variety of skeletal, ligamentous, and muscular problems. Orthopaedics are involved in the management of a newborn's dislocated hip, a teenager's curved spine, an athlete's injury knee, a motor vehicle accident victim, an adult's worn-out joint, and an elderly woman's fracture hip.

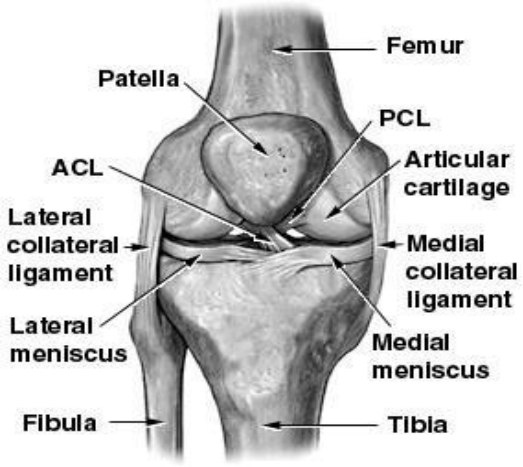
The musculoskeletal system is a complex biomechanical organ. It is constantly responding to the demands of the patient. Bone is in constant turnover. It atrophies when not used, and hypertrophies when stressed. Overall bone mass is increased until some time between 30 and 35 years of age, after which there is an overall decrease of bone as a consequence of more resorption than production. Bone can heal without leaving a scar. Articular cartilage is a special material because it has properties that people have not been able to reproduce. It is a wonderful shock absorber, yet when sliding with another surface of articular cartilage bathed in normal synovial fluid, the constant of friction is a fraction of that found with ice-on-ice. Unfortunately, upon reaching adulthood, the ability to generate new articular cartilage ceases and as it wears out or is injured, it is not replaced. Repair fibrocartilage, metal, and plastic are the materials currently substituted for articular cartilage. Skeletal muscle accounts for almost 50% of the body's weight making it the single largest tissue mass in the human body. There is one basic structural unit in muscle fiber; however, the arrangement of these fibers varies depending on a particular muscle's function. Muscle fibers are either parallel or oblique with oblique fibers existing in various configurations.



Skeletal Growth and Physiology

The skeletal system is initially formed as cartilage with the exception of the craniofacial

bones and clavicle. These bones do not have a cartilaginous analogue and are formed directly from membranous tissue. The process of bone formation without an intermediate cartilage form is called intramembranous bone formation. The majority of an adult's bone is formed by intramembranous bone formation because diaphyseal bone grows circumferentially by the apposition of bone by the surrounding periosteum without cartilage being produced. Enchondral ossifications is the formation of bone through the initial formation of a cartilage model that then becomes bone. The skeletal system is formed in utero as cartilage; however, prior to birth, some of these prebone structures are well on their way to bone formation. This happens first in the middle of the diaphysis, known as the primary center of ossification. Later, at the secondary ossification center, bone will begin to form at the ends of the prebone structures. The secondary center of ossification has articular cartilage surrounding it on the side facing the joint and epiphyseal cartilage on the side facing the primary ossification center. The bone grows in length through the epiphyseal growth plate, which produces cartilage that undergoes enchondral ossification.



The epiphyseal growth plate is made up of proliferating cartilage cells that eventually die. After the cartilage cells die, osteoblasts line the calcified cartilage matrix previously produced by the chondrocytes, thus forming bone. The epiphyseal growth plate is divided into zones. The number of zones often varies in the literature dependent upon the author; however, a general consensus specifies five zones. The first zone is the resting or reserve zone, followed by the proliferative zone, the maturation zone, the degeneration zone, and the zone of calcification. The zones of maturation, degeneration, and calcification are often referred to as the hypertrophic zone. The initial bone formed consists of spicules of bone with a calcified cartilaginous core and is called the primary spongiosa. The calcified cartilage will be removed entirely as the bone continues to remodel. The area of the bone with the primary spongiosa is called the metaphysis. This bone remodels to become the narrower diaphysis. The initial bone formed during this process is referred to as woven bone. This bone is unorganized both grossly and microscopically. As it remodels and matures, it becomes lamellar bone. It can be either cortical bone with a blood supply and a Haversian system, or trabecular bone, which does not have a Haversian system

Bone is produced by osteoblasts, which become osteocytes once they are trapped within a matrix of bone. Osteoclasts are multinucleated cells that have the capability of resorbing bone. Osteoblast and osteocytes are recognized under the microscope by the matrix they produce. Chondrocytes are cells responsible for making cartilage and live within the cartilage matrix. (Use of the term chondroblast for the cartilage-producing cells lining a surface of cartilage production is appropriate, but rarely used.)

Bone remodels constantly, primarily under the influence of a mechanical load. During the first 30 years of life, a person's overall skeletal mass perpetually increases; however, after 30

years of age, overall skeletal mass decreases, with women experiencing a period of accelerated loss just after menopause (Fig. 42-4). The more bone an individual has acquired by age 30, the less likely she or he are to develop osteoporosis.

Reading 2

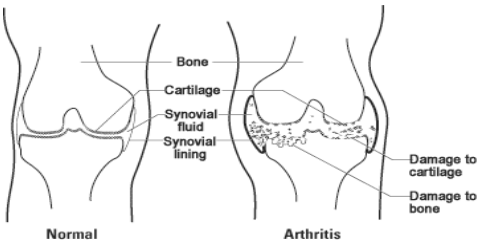
Approach to Articular and Musculoskeletal Disorders: from Harrison's 18th Edition

Introduction

Musculoskeletal complaints account for >315 million outpatient visits per year and nearly 20% of all outpatient visits in the United States. The Centers for Disease Control and Prevention estimate that 22% (46 million) of the U.S. population has physician-diagnosed arthritis and 19 million have significant functional limitation. While many patients will have self-limited conditions requiring minimal evaluation and only symptomatic therapy and reassurance, specific musculoskeletal presentations or their persistence may herald a more serious condition that requires further evaluation or laboratory testing to establish a diagnosis. The goal of the musculoskeletal evaluation is to formulate a differential diagnosis that leads to an accurate diagnosis and timely therapy, while avoiding excessive diagnostic testing and unnecessary treatment There are several urgent conditions that must be diagnosed promptly to avoid significant morbid or mortal sequelae. These "red flag" diagnoses include septic arthritis, acute crystal-induced arthritis (e.g., gout), and fracture. Each may be suspected by its acute onset and monarticular or focal musculoskeletal pain.

Individuals with musculoskeletal complaints should be evaluated with a thorough history, a comprehensive physical and musculo-skeletal examination, and, if appropriate, laboratory testing. The initial encounter should determine whether the musculoskeletal complaint signals a red flag condition (septic arthritis, gout, or fracture) or not. The evaluation should proceed to ascertain if the complaint is (1) *articular* or *nonarticular* in origin, (2) *inflammatory* or *noninflammatory* in nature, (3) *acute* or *chronic* in duration, and (4) *localized (monarticular)* or *widespread* (*polyarticular*) in distribution.

With such an approach and an understanding of the pathophysiologic processes, the musculoskeletal complaint or presentation can be characterized (e.g., acute inflammatory monarthritis or a chronic noninflammatory, nonarticular widespread pain) to narrow the diagnostic possibilities. A diagnosis can be made in the vast majority of individuals. However, some patients will not fit immediately into an established diagnostic category. Many musculoskeletal disorders resemble each other at the outset, and some may take weeks or months to evolve into a readily recognizable diagnostic entity. This consideration should temper the desire to establish a definitive diagnosis at the first encounter.



Knee Pain

Knee pain may result from intraarticular (OA, RA) or periarticular (anserine bursitis, collateral ligament strain) processes or be referred from hip pathology. A careful history should delineate the chronology of the knee complaint and whether there are predisposing conditions, trauma, or medications that might underlie the complaint. For example, patellofemoral disease (e.g., OA) may cause anterior knee pain that worsens with climbing stairs. Observation of the patient's gait is also important. The knee should be carefully inspected in the upright (weight-bearing) and prone positions for swelling, erythema, malalignment, visible trauma (contusion, laceration), or muscle wasting. The most common form of malalignment in the knee is *genu varum* (bowlegs) or *genu valgum* (knock-knees). Bony swelling of the knee joint commonly results from hypertrophic osseous changes seen with disorders such as OA and neuropathic arthropathy. Swelling caused by hypertrophy of the synovium or synovial effusion may manifest as a fluctuant, ballotable, or soft tissue enlargement in the suprapatellar pouch (suprapatellar reflection of the synovial cavity) or regions lateral and medial to the patella. Synovial effusions may also be detected by balloting the patella downward toward the femoral groove or by eliciting a "bulge sign." With the knee extended the examiner should manually compress, or "milk," synovial fluid down from the suprapatellar pouch and lateral to the patellae. The application of manual pressure lateral to the patella may cause an observable shift in synovial fluid (bulge) to the medial aspect. The examiner should note that this maneuver is only effective in detecting small to moderate effusions (<100 mL). Inflammatory disorders such as RA, gout, pseudogout, and reactive arthritis may involve the knee joint and produce significant pain, stiffness, swelling, or warmth. A popliteal or *Baker's cyst* is best palpated with the knee partially flexed and is best viewed posteriorly with the patient standing and knees fully extended to visualize isolated or unilateral popliteal swelling or fullness.

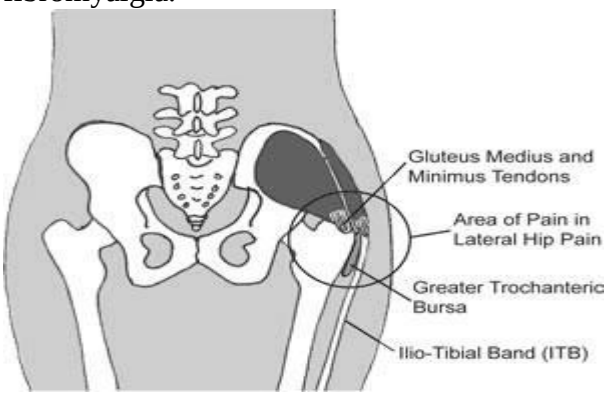
Anserine bursitis is an often missed periarticular cause of knee pain in adults. The pes anserine bursa underlies the insertion of the conjoined tendons (sartorius, gracilis, semitendinosis) on the anteromedial proximal tibia and may be painful following trauma, overuse, or inflammation. It is often tender in patients with fibromyalgia, obesity, and knee osteoarthritis. Other forms of bursitis may also present as knee pain. The prepatellar bursa is superficial and is located over the inferior portion of the patella. The infrapatellar bursa is deeper and lies beneath the patellar ligament before its insertion on the tibial tubercle.

Internal derangement of the knee may result from trauma or degenerative processes. Damage to the meniscal cartilage (medial or lateral) frequently presents as chronic or intermittent knee pain. Such an injury should be suspected when there is a history of trauma, athletic activity, or chronic knee arthritis, and when the patient relates symptoms of "locking," clicking, or "giving way" of the joint. With the knee flexed 90° and the patient's foot on the table, pain elicited during palpation over the joint line or when the knee is stressed laterally or medially may suggest a meniscal tear. A positive McMurray test may also indicate a meniscal tear. To perform this test, the knee is first flexed at 90°, and the leg is then extended while the lower extremity is simultaneously torqued medially or laterally. A painful click during inward rotation may

indicate a lateral meniscus tear, and pain during outward rotation may indicate a tear in the medial meniscus. Lastly, damage to the cruciate ligaments should be suspected with acute onset of pain, possibly with swelling, a history of trauma, or a synovial fluid aspirate that is grossly bloody. Examination of the cruciate ligaments is best accomplished by eliciting a drawer sign. With the patient recumbent, the knee should be partially flexed and the foot stabilized on the examining surface. The examiner should manually attempt to displace the tibia anteriorly or posteriorly with respect to the femur. If anterior movement is detected, then anterior cruciate ligament damage is likely. Conversely, significant posterior movement may indicate posterior cruciate damage. Contralateral comparison will assist the examiner in detecting significant anterior or posterior movement.

Hip Pain

The hip is best evaluated by observing the patient's gait and assessing range of motion. The vast majority of patients reporting "hip pain" localize their pain unilaterally to the posterior gluteal musculature. Such pain tends to radiate down the posterolateral aspect of the thigh and may or may not be associated with complaints of low back pain. This presentation frequently results from degenerative arthritis of the lumbosacral spine or disks and commonly follows a dermatomal distribution with involvement of nerve roots between L4 and S1. Sciatica is caused by impingement of the L4, L5, or S1 nerve (i.e., from a herniated disk) and manifests as unilateralneuropathic pain extending from the gluteal region down the posterolateral leg to the foot. Some individuals instead localize their "hip pain" laterally to the area overlying the trochanteric bursa. Because of the depth of this bursa, swelling and warmth are usually absent. Diagnosis of trochanteric bursitis can be confirmed by inducing point tenderness over the trochanteric bursa. Gluteal and trochanteric pain may also indicate underlying fibromyalgia.

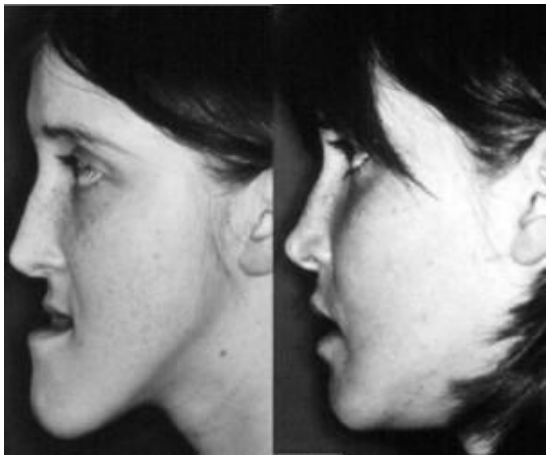


Range of movement may be limited by pain. Pain in the hip joint is less common and tends to be located anteriorly, over the inguinal ligament; it may radiate medially to the groin. Uncommonly, ilio-psoas bursitis may mimic true hip joint pain. Diagnosis of iliopsoas bursitis may be suggested by a history of trauma or inflammatory arthritis. Pain associated with iliopsoas bursitis is localized to the groin or anterior thigh and tends to worsen with hyperextension of the hip; many patients prefer to flex and externally rotate the hip to reduce the pain from a distended bursa

Unit 16: Plastic and Reconstructive Surgery

Reading 1

Plastic surgery is derived from the Greek word, "plastikos," meaning *to mold*. The discipline endeavors to reconstruct all manner of defects and deformities. Central to this enterprise is a precise knowledge of anatomy, respect for surgical technique, and finesse, and a keen, creative sense for the possibilities inherent in the manipulation and remodeling of tissue.



Historically, the premise for plastic surgery dates back several millennia and spans many cultures. The Egyptian, "Edwin Smith papyrus," believed to be written in 1700 B.C. heralds modern fastidiousness with wound care, emphasizing the importance of débridement and meticulous surgical technique. The *Sushruta Samita*, an Indian text written in 500 B.C., records the first description of a pedicled flap for nasal reconstruction. The Roman physician Celsus gave detailed treatment guidelines for diverse facial injuries during the first century. 1 With a decline in the advancement of Western medicine in the post-Roman era, the Near Eastern physicians were advancing sophisticated surgical techniques. The Renaissance brought a resurgence in empiric medicine and creative surgical approaches to reconstruction: Tagliacozzi's text, *per Insitonem* (1597), is a prescient text which gives a permutation of the Indian forehead flap with a medial arm flap for nose amputations. 2

The unfortunate circumstance of internecine conflicts during World Wars I and II stimulated the evolution of plastic surgery by forcing surgeons to grapple with complex, massive, traumatic defects of the maxillofacial region and extremities. Gillies made an exhaustive exploration of head and neck anatomy to recreate bony and soft-tissue defects wrought by escalating weaponry. Concordantly, there was an increasing realization that the reconstructive challenge crossed traditional boundaries of the surgical disciplines of orthopedics, general surgery, oral surgery, and head and neck surgery. An actual organizing entity for plastic surgery was not created until 1937 with the formation of the American Board of Plastic Surgery.

Even as the field was coalescing as a distinct surgical discipline, the accelerating pace of medical innovation was producing subspecialization in the field. Paul Tessier aggressively pursued new ways of shaping deformities in the craniofacial skeleton. Harry Buncke and Nakayama germinated the technical and physiologic basis for microsurgery. Pioneers such as Macgregor and

Jackson carefully engaged the anatomic underpinnings of flaps and gave a systematic rationale for future investigation into all manner of soft-tissue coverage.

Concomitantly, plastic surgery applied principles vital to the issue of reconstruction, aesthetic rejuvenation, and enhancement. Cronin and Gerow fathered the invention of breast implants in 1962, which, in turn, ignited both a specific interest in breast cosmesis, as well as a general interest in applying alloplastic materials to plastic surgery.
Wound Healing

Much of plastic surgery is predicated on the fundamentals of wound healing and tissue regeneration. Understanding the mechanophysiology of healing and its relationship to surgical technique are paramount to the plastic surgeon's endeavors. While a detailed treatise on wound healing is covered in another section, certain basic concepts are important to emphasize.

There are three general types of wound healing. The first is *primary* wound healing, which is characterized by the occurrence of mechanical apposition of wound edges and a cascade of inflammatory cell activation. This recruitment creates a milieu which allows re-epithelialization and collagen strengthening to occur. The second, *delayed primary* healing, occurs when the wound healing process is potentially compromised by incipient infection. With this type of healing, the surgeon may opt to leave the soft tissue unapposed and allow native inflammation and external débridement to cleanse the wound. If, on evaluation several days later, the wound appears uninfected, the wound can then be closed and the normal process of primary healing can then be re-initiated. Third is *secondary* healing, which is recommended for a wound that does not show potential for early closure. The wound can be allowed to close over time by the processes of inflammation, contraction (via myofibroblasts), and eventual re-epithelialization.

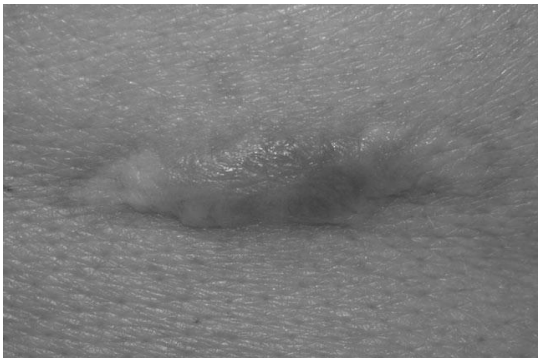
An important corollary to timely and robust wound healing is the appropriate interaction among inflammatory cells such as polymorphonuclear neutrophils, macrophages, lymphocytes, fibroblasts, and the bath of cytokines, such as interleukins, interferons, transforming growth factor, platelet-derived growth factor, epidermal growth factor, and fibroblast growth factors. Critical to the overarching success of inflammation and wound healing is the establishment of new vessels or angiogenesis. The fundamental limiting step to both wound healing and tissue reconstruction is the presence of adequate vascularity.

Reading 2

Impaired Wound Healing

If the necessary blood supply to a healing region is compromised, then wound healing can be delayed. Similarly, the relative paucity of the basic constituents of inflammatory cytokines or matrix components (vitamins, zinc, copper, iron) may result in structural weakness of the wound. Radiation is often an issue for reconstruction of ablative defects. Among other effects, radiation can create local ischemic conditions via microangiopathic damage. Moreover, the inherent ability for the tissue to regenerate is altered in both an acute and delayed fashion. Diabetic patients can also experience impaired wound healing as a consequence of the changes in glucose metabolism and insulin regulation that occurs systemically.

Dysfunctional healing can also manifest as abnormal scars. Hypertrophic scars and keloids are manifestations of altered collagen deposition and breakdown. Hypertrophic scars are raised, collagen-rich lesions that do not go beyond the initial boundaries of the insult, whereas keloids are scars that have progressed beyond these boundaries. It is difficult to distinguish these two pathologic entities by routine histology, although it is believed that keloids may have thicker collagen fibers and a greater degree of hyaluronic acid in the epidermis than hypertrophic scars.



Hypertrophic scars and keloids

Treatment of scars includes pressure, silicone sheet and gels, and intralesional corticosteroids. Topical vitamins A and E are used for treatment of unsightly scars, but no definitive clinical trials have demonstrated their efficacy. For intractable keloids, radiation therapy in conjunction with surgical excision has led to a 50 to 80% reduction in keloids.

Basic Technique of Skin Closure

Notwithstanding the advent of tissue adhesives such as cyanoacrylate, suture closure remains the most common and durable technique of creating precise skin closure. The choice of suture material can vary from monofilament to polyfilament and absorbable to nonabsorbable. Regardless of the suture material used, the notion of minimizing tension is critical to maintaining wound closure and preventing excessive scar formation. This objective can be accomplished by using dermal and subdermal sutures to diffuse the tension among multiple layers. Another way of ameliorating the tension effect on wounds is to align skin incisions along lines of minimal tension, otherwise known as relaxed-skin tension lines

Unit 17: The Biology of Aging

from Harrison's 18th Edition

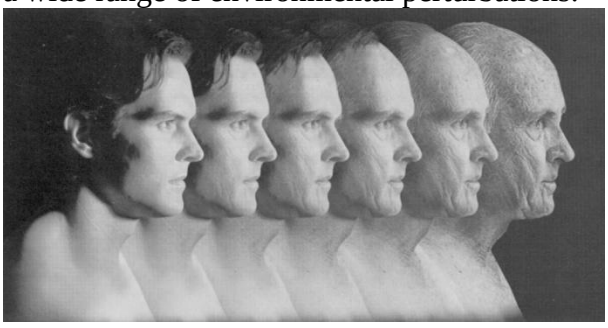
Reading 1

Introduction

Thanks largely to the power of genetic analysis in model organisms such as *Caenorhabditis elegans* (a nematode), *Drosophila melanogaster* (a fruit fly), and the laboratory mouse, major advances have been made in the elucidation of what can be termed "public" modulations of intrinsic biological aging—that is to say, commonalities of gene actions across widely diverse phyla that explain, in part, the plasticity of processes of aging. There are hints that at least one such conserved pathway may be operative in our own species. These observations, together with related research on other biochemical pathways, a long history of research on the beneficial effects of dietary restriction (most recently including an initial report of its beneficial effects on healthspan and lifespan in a primate), and spectacular advances in genomics raise the possibility that we may one day be able to delay the times of onset and decrease the rates of progression of aging processes. Such interventions have the potential to extend the healthspans and, therefore, the functional lifespans of a large proportion of our population. This new knowledge, however, is still very distant from clinical translation. Many remain skeptical of the relevance of these experimental findings. Moreover, we need much more information on the pathophysiology of aging, especially in the invertebrate models that have provided most of our new knowledge concerning genetic modulations of lifespan. We will also require more detailed information on the impact of longevity enhancements upon what can be described as the "terminal decline" of the life course, the stage of life in humans responsible for protracted morbidity, frailty, and the consequent loss of the ability to live independently. These terminal declines account for a very substantial proportion of all health care costs. Finally, the promising new knowledge needs fuller discussions by ethicists, economists, sociologists, and political scientists, among others, as to the impacts upon society of any large-scale clinical translations.

Definitions of Aging: Senescent Phenotypes

Mammalian gerontologists usually define aging in terms of the gradual, insidious, and progressive declines in structure and function (involving molecules, cells, tissues, organs, and organisms) that begin to unfold after the achievement of sexual maturity. These declines affect the germ line as well as the soma. For large populations of individuals, exponential declines in the probability of survival are observed. The aging organism is less successful in its reaction to injury and has increasing difficulties in maintaining physiological homeostasis. The organism, therefore, becomes increasingly vulnerable to a wide range of environmental perturbations.



Biological aging is the major risk factor for essentially all of the major geriatric disorders, including dementias of the Alzheimer type (DAT), Parkinson's disease, age-related macular degeneration, ocular cataracts, presbycusis, all forms of arteriosclerosis, type 2 diabetes mellitus, congestive heart failure, sarcopenia, osteoporosis, osteoarthritis, degenerative intervertebral disk disease, immunosenescence, benign prostatic hyperplasia, and most forms of cancer. These and many other disorders can be referred to as "senescent phenotypes."

Reading 2

How to remain young (Internet source)

Is aging skin preventable? Sure, if you believe the ads for products that claim to slow the aging process. But how much is your aging skin really under your control?

With age, the skin suffers natural wear-and-tear, just like the rest of our bodies. But much of what we think of as natural aging is in fact due to sun exposure and other factors. That means it can be avoided -- and it's never too late to start.

Normal Aging of Skin: Collagen, Elastin, and Sagging Skin

Underlying our skin is a fiber meshwork of collagen and elastin -- proteins that keep skin firm. When skin is stretched, this protein matrix snaps it back into place.

As we age, the fiber network weakens, and skin sags as it loses its support structure. Other unavoidable forces contribute to aging skin, as well:

- Skin becomes thinner with age, and loses fat. The plump smoothness of our skin as children is replaced by a rougher texture.
- Gravity relentlessly tugs on weakened skin, creating the droop of jowls or "chicken fat" under the arms.
- Our genetic code contributes invisibly to the process -- leading to skin that looks 50 at 80 in some people, the unfortunate reverse in others.

None of this so-called "intrinsic aging" of skin can be avoided. But did you notice we haven't said anything yet about wrinkles?

Preventable Aging of Skin: Sun Damage

In fact, most of the skin changes associated with aging are avoidable. And most of them are due to one cause: sun damage. The ultraviolet rays from the sun penetrate into the skin. There, they damage the elastic fibers that keep skin firm, allowing wrinkles to develop. Sunlight is also responsible for age spots or "liver spots" on the hands, face, and other sun-exposed areas. The amount of wrinkles that develop, and how prominent they are, are largely dependent on a person's lifetime sun exposure. While we can't go back and put sunscreen on our carefree 10-year-old selves, we can stop the damage that's happening now:

- Stop intentionally sunbathing. Any suntan means skin damage has occurred.
- Always wear sunscreen. Choose a product with sun protection factor (SPF) 15 or greater. The hands and face are the most frequently exposed -- cover them.
- Wear a hat with a brim.
- Avoid the sun between 10 a.m. and 3 p.m., when its rays are the strongest.

Even with perfect sunscreen use, wrinkles can't be prevented completely. Some wrinkling is hereditary, and a certain amount of wrinkles are natural to aging.

Besides preventing sun damage, other habits can age skin prematurely. Slow the aging process by eliminating these skin wrinklers.

How Smoking Damages Skin and Causes Wrinkles

Wrinkles occur sooner and run deeper in people who smoke, leading to so-called "smoker's face." Decreased blood flow to the face, and damage from toxic chemicals in smoke, are the likely causes. In addition, smokers tend to squint to keep smoke from their eyes, which can cause wrinkles.

Crow's feet around the eyes, and droopy skin around the eyelids ("smoker's face") are common in long-time tobacco smokers. A desire to protect your youthful looks is one more good reason to quit smoking. Premature aging skin is not inevitable -- no matter what your parents looked like.

Excessive Drinking and Your Skin

Excessive alcohol (more than one drink a day for women, two for men) is bad for skin, and your health in general. People who drink heavily tend to not eat a healthy diet -- depriving skin of the nutrients it needs to prevent aging.

The Diet and Skin Connection

Skin is constantly fighting a battle with the sun, and constantly repairing and regenerating itself. Your skin needs the right nutrition to stay young and healthy looking. If you're eating lots of junk food, you're feeding your skin junk, too.

Antioxidants like vitamin C and E, as well as vitamin A and the B vitamin biotin, are particularly important for healthy skin. You'll get all of these nutrients, and more, by eating five to seven servings of fresh fruits and vegetables each day. Tomatoes, citrus, green leafy vegetables, and carrots are a good place to start.

Our parents gave us many gifts. Maybe the genes for good skin were one of yours. But no matter what kind of skin you inherited, you can take action to keep the skin you have looking young.

Translation

The Classical Evolutionary Biological Theory of Why We Age

A compelling theory as to why aging occurs has been developed by a series of contributions by evolutionary biologists, beginning with JBS Haldane. Haldane wondered why certain late-onset disorders, such as Huntington's disease, seemed to be so prevalent in England—perhaps of the order of one per thousand instead of what might have been expected from germ-line mutation rates—perhaps one per million. He concluded that this was because the disease had largely escaped the force of natural selection, because the commonest forms of the disease did not manifest until after reproduction had ceased. In age-structured populations (i.e., populations consisting of individuals with a wide range of ages), most of the reproduction is carried out by the younger cohorts. This is because, historically, few individuals living in the wild escaped the effects of infections, predation, nutritional deprivations, and accidents to achieve old age. As such, even late-acting *good* alleles will have only minor contributions to the gene pools of subsequent generations. Peter Medawar extended this idea, arguing that there are numerous such constitutional mutations, an idea that has come to be known as the "mutation accumulation" theory of aging. (These are mutations that one is born with, not somatic mutations.) By this argument, most of us are likely to have been born with some special vulnerability to a late-life disorder or disorders. A second major theory, known as "antagonistic pleiotropy," was developed by George C. Williams. He argued that there are likely to be many genetic alleles that were selected because of their enhancement of reproductive fitness *early* in the life course, but that have negative effects *late* in life, when the force of natural selection will have greatly diminished. A more general conceptualization of tradeoffs between reproduction and lifespan (the "disposable soma" theory) was developed by TBL Kirkwood. The evolutionary theory was quantified by

William D. Hamilton and elaborated on by Brian Charlesworth and Michael Rose.

Perhaps the best indication that the field of biogerontology has finally matured as a science is the fact that its most cherished theory, what can now be termed as the "classical" evolutionary theory, has undergone several challenges. First, demographers have noted that at the extremes of old age for organisms as diverse as roundworms, fruit flies, med flies, and humans, rates of *declines* in the force of natural selection diminish. One response to this important challenge (the "cocoon" hypothesis) is that these declines may simply be related to the virtual cessation of locomotor activities at extreme ages. When flies cease flying and worms cease moving, fewer opportunities for serious injuries may result. These "plateaus" in the rates of mortality at very advanced ages are much less striking for people; they might also be related, in part, to diminished motility, as well as to secular trends in the development of central heating, air conditioning, and immunizations. A second challenge comes from geneticists who have discovered that, to our great surprise, many single-gene mutations can substantially increase the lifespans of Baker's yeast, nematodes, and fruit flies This issue has been most systematically explored in *C. elegans*; a meta-analysis of an initial set of unbiased, genome-wide RNAi screens ("knockdowns," but not "knockouts" of gene expression) has tabulated hundreds of single-gene loci capable of enhancing lifespan when they are dialed down. These genes fall into a finite number of pathways and, moreover, many of them fit within the context of antagonistic pleiotropic mechanisms of aging. For example, hypomorphic mutations in genes within the most famous of these pathways, the insulin-like growth factor (IGF)/insulin signaling pathway, may be reporting on an evolutionarily conserved diapause—nature's way of taking time out from the business of development and reproduction during hard times, such as severe shortages of food. The gene actions associated with such diapauses (many of which are still unexplored at the biochemical genetic level) understandably result in enhanced resistance to various stresses. A large number of these *C. elegans* "longevity genes" converge upon a single transcription factor, *daf2*, or influence mitochondrial function. Moreover, it is possible that many such genes may be specific for this highly inbred laboratory model. In general, these investigations support, rather than refute, the evolutionary theory of aging.

A third challenge to the theory comes mainly from anthropologists and economists and emphasizes intergenerational transfers of resources. As an oversimplification, this idea is often referred to as "the grandmother hypothesis." Older members of population groups have survived a number of threats to their existence and can pass along to their younger family members information about successful avoidance or adaptation. Field experiments with prides of lions and olive baboons have failed to support this hypothesis. Moreover, while many grandparents are now contributing to the reproductive fitness of their children and grandchildren via transfer of resources, current evidence, while still incomplete, indicates that such elders were exceedingly rare within populations of our remote ancestors, when the evolution of species-specific gene actions would have evolved. Any such favorable alleles not expressed until those late stages of life would, therefore, have been vastly diluted by the alleles of their progeny.

A final challenge to evolutionary theory comes from a reexamination of the assumptions made by Hamilton in his influential 1966 paper. Baudisch, using different assumptions, demonstrates that, under some conditions, the force of natural selection can *increase* during aging. For example, species of rockfish that continue to grow beyond sexual maturity are much more likely to become predators rather than prey; as such, the force of natural selection would, indeed, become stronger, not weaker, as they age.

The message is that aging is *non-adaptive*. It did not evolve via a program of determinative gene actions that are designed to lead to the death of aging organisms because it is good for the species.

Unit 18: Chronic Pain

Reading 1

Managing patients with chronic pain is intellectually and emotionally challenging. The patient's problem is often difficult or impossible to diagnose with certainty; such patients are demanding of the physician's time and often appear emotionally distraught. The traditional medical approach of seeking an obscure organic pathology is usually unhelpful. On the other hand, psychological evaluation and behaviorally based treatment paradigms are frequently helpful, particularly in the setting of a multidisciplinary pain-management center. Unfortunately, this approach, while effective, remains largely underused in current medical practice.

There are several factors that can cause, perpetuate, or exacerbate chronic pain. First, of course, the patient may simply have a disease that is characteristically painful for which there is presently no cure. Arthritis, cancer, chronic daily headaches, fibromyalgia, and diabetic neuropathy are examples of this. Second, there may be secondary perpetuating factors that are initiated by disease and persist after that disease has resolved. Examples include damaged sensory nerves, sympathetic efferent activity, and painful reflex muscle contraction. Finally, a variety of psychological conditions can exacerbate or even cause pain.

There are certain areas to which special attention should be paid in a patient's medical history. Because depression is the most common emotional disturbance in patients with chronic pain, patients should be questioned about their mood, appetite, sleep patterns, and daily activity. A simple standardized questionnaire, such as the Beck Depression Inventory, can be a useful screening device. It is important to remember that major depression is a common, treatable, and potentially fatal illness.

Other clues that a significant emotional disturbance is contributing to a patient's chronic pain complaint include pain that occurs in multiple, unrelated sites; a pattern of recurrent, but separate, pain problems beginning in childhood or adolescence; pain beginning at a time of emotional trauma, such as the loss of a parent or spouse; a history of physical or sexual abuse; and past or present substance abuse.

On examination, special attention should be paid to whether the patient guards the painful area and whether certain movements or postures are avoided because of pain. Discovering a mechanical component to the pain can be useful both diagnostically and therapeutically. Painful areas should be examined for deep tenderness, noting whether this is localized to muscle, ligamentous structures, or joints. Chronic myofascial pain is very common, and, in these patients, deep palpation may reveal highly localized trigger points that are firm bands or knots in muscle. Relief of the pain following injection of local anesthetic into these trigger points supports the diagnosis. A neuropathic component to the pain is indicated by evidence of nerve damage, such as sensory impairment, exquisitely sensitive skin, weakness, and muscle atrophy, or loss of deep tendon reflexes. Evidence suggesting sympathetic nervous system involvement includes the presence of diffuse swelling, changes in skin color and temperature, and hypersensitive skin and joint tenderness compared with the normal side. Relief of the pain with a sympathetic block is diagnostic.

A guiding principle in evaluating patients with chronic pain is to assess both emotional and organic factors before initiating therapy. Addressing these issues together, rather than

waiting to address emotional issues after organic causes of pain have been ruled out, improves compliance in part because it assures patients that a psychological evaluation does not mean that the physician is questioning the validity of their complaint. Even when an organic cause for a patient's pain can be found, it is still wise to look for other factors. For example, a cancer patient with painful bony metastases may have additional pain due to nerve damage and may also be depressed. Optimal therapy requires that each of these factors be looked for and treated.

Reading 2

Treatment: Chronic Pain

Once the evaluation process has been completed and the likely causative and exacerbating factors identified, an explicit treatment plan should be developed. An important part of this process is to identify specific and realistic functional goals for therapy, such as getting a good night's sleep, being able to go shopping, or returning to work. A multidisciplinary approach that uses medications, counseling, physical therapy, nerve blocks, and even surgery may be required to improve the patient's quality of life. There are also some newer, relatively invasive procedures that can be helpful for some patients with intractable pain. These include image-guided interventions such as epidural injection of glucocorticoids for acute radicular pain, radiofrequency treatment of the facet joints for chronic facet-related pain, percutaneous intradiscal treatments for both axial and radicular pain, and placement of implanted intraspinal electrodes and implantation of intrathecal drug-delivery systems for severe and persistent pain that is unresponsive to more conservative treatments. There are no set criteria for predicting which patients will respond to these procedures. They are generally reserved for patients who have not responded to conventional pharmacologic approaches. Referral to a multidisciplinary pain clinic for a full evaluation should precede any invasive procedures. Such referrals are clearly not necessary for all chronic pain patients. For some, pharmacologic management alone can provide adequate relief.

Translation

Treatment of Neuropathic Pain

It is important to individualize treatment for patients with neuropathic pain. Several general principles should guide therapy: the first is to move quickly to provide relief, and the second is to minimize drug side effects. For example, in patients with postherpetic neuralgia and significant cutaneous hypersensitivity, topical lidocaine (Lidoderm patches) can provide immediate relief without side effects. Anticonvulsants (gabapentin or pregabalin, see above) or antidepressants (nortriptyline, desipramine, duloxetine, or venlafaxine) can be used as first-line drugs for patients with neuropathic pain. Systemically administered antiarrhythmic drugs such as lidocaine and mexiletene are less likely to be effective; although intravenous infusion of lidocaine predictably provides analgesia in those with many forms of neuropathic pain, the relief is usually transient, typically lasting just hours after the cessation of the infusion. The oral lidocaine congener mexiletene is poorly tolerated, producing frequent gastrointestinal adverse effects. There is no consensus on which class of drug should be used as a first-line treatment for any chronically painful condition. However, because relatively high doses of anticonvulsants are required for pain relief, sedation is very common. Sedation is also a problem with TCAs but is much less of a problem with serotonin/norepinephrine reuptake inhibitors (SNRIs, e.g., venlafaxine and duloxetine). Thus, in the elderly or in those patients whose daily activities require high-level mental activity, these drugs should be considered the first line. In contrast, opioid medications should be used as a second- or third-line drug class. While highly effective for many painful conditions, opioids are sedating, and their effect tends to lessen over time, leading to dose escalation and, occasionally, a worsening of pain due to physical dependence. Drugs of different classes can be used in combination to optimize pain control.

The End!