Specialized English One

School of Medicine

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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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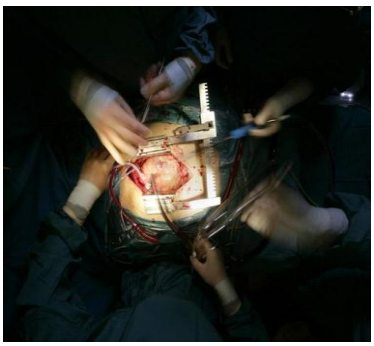
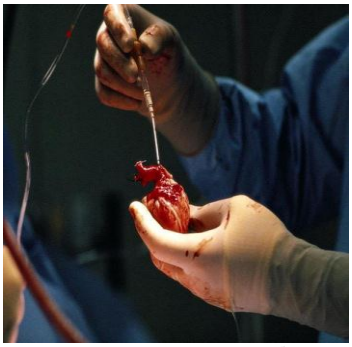
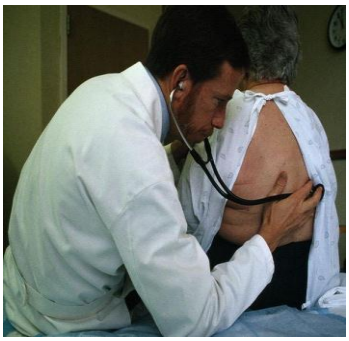
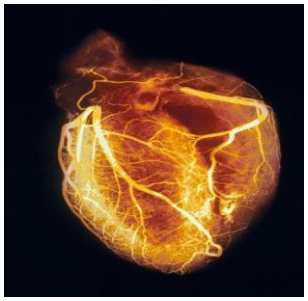
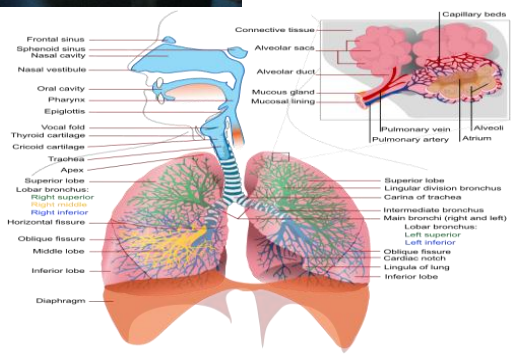






Unit 1: Introduction to Medical Practice

Reading 1

The Modern-Day Physician

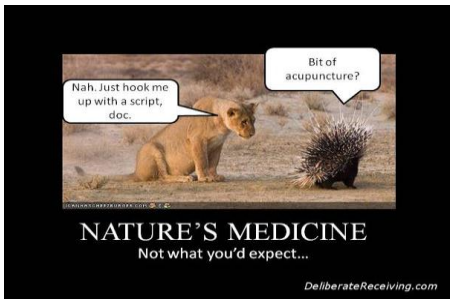
> *No greater opportunity, responsibility, or obligation can fall to the lot of a human being than to become a physician. In the care of the suffering, [the physician] needs technical skill, scientific knowledge, and human understanding.… Tact, sympathy, and understanding are expected of the physician, for the patient is no mere collection of symptoms, signs, disordered functions, damaged organs, and disturbed emotions. [The patient] is human, fearful, and hopeful, seeking relief, help, and reassurance.*
>
> *– Harrison's Principles of Internal Medicine, 1950*

The practice of medicine has changed in significant ways since the first edition of Harrison's book appeared in 1950. The advent of molecular biology with its enormous implications for the biological sciences (the sequencing of the human genome), sophisticated new imaging techniques, and advances in bioinformatics and information technology have contributed to an explosion of scientific information that has fundamentally changed the way we define, diagnose, treat, and prevent disease. This explosion of scientific knowledge is not at all static as it continues to intensify with time.

The widespread use of electronic medical records and the Internet have altered the way we practice medicine and exchange information. As today's physician struggles to integrate the copious amounts of scientific knowledge into everyday practice, it is important to remember that the ultimate goal of medicine is to treat the patient. Despite more than 50 years of scientific advances since the first edition of this text, it is critical to underscore that cultivating the intimate relationship that exists between physician and patient still lies at the heart of successful patient care.

The Science and Art of Medicine

Science-based technology and deductive reasoning form the foundation for the solution to many clinical problems. Spectacular advances in biochemistry, cell biology, and genomics, coupled with newly developed imaging techniques, allow access to the innermost parts of the cell and provide a window to the most remote recesses of the body. Revelations about the nature of genes and single cells have opened the portal for formulating a new molecular basis for the physiology of systems. Increasingly, we are understanding how subtle changes in many different genes can affect the function of cells and organisms. We are beginning to decipher the complex mechanisms by which genes are regulated. We have developed a new appreciation of the role of stem cells in normal tissue function and in the development of cancer, degenerative disease, and other disorders. The knowledge gleaned from the science of medicine has al-ready improved and undoubtedly will further improve our under-standing of complex disease processes and provide new approaches to disease treatment and prevention. Yet skill in the most sophisticated application of laboratory technology and in the use of the latest therapeutic modality alone does not make a good physician.



When a patient poses challenging clinical problems, an effective physician must be able to identify the crucial elements in a complex history and physical examination, to order the appropriate laboratory tests, and to extract the key results from the crowded computer print-outs of data to determine whether to "treat" or to "watch." Deciding whether a clinical clue is worth pursuing or should be dismissed as a "red herring" and weighing whether a proposed treatment entails a greater risk than the disease itself are essential judgments that the skilled clinician must make many times each day. This combination of medical knowledge, intuition, experience, and judgment defines the ***art of medicine***, which is as necessary to the practice of medicine as is a sound scientific base.

Evidence-Based Medicine

Evidence-based medicine refers to the concept that clinical decisions are formally supported by data, preferably data that are derived from prospectively designed, randomized, controlled clinical trials. This is in sharp contrast to anecdotal experience, which may often be biased. Unless they are attuned to the importance of using larger, more objective studies for making decisions, even the most experienced physicians can be influenced by recent encounters with selected patients. Evidence-based medicine has become an increasingly important part of the routine practice of medicine and has led to the publication of a number of practice guidelines.

Practice Guidelines

Professional organizations and government agencies are developing formal clinical-practice guidelines to aid physicians and other caregivers in making diagnostic and therapeutic decisions that are evidence-based, cost-effective, and most appropriate to a particular patient and clinical situation. As the evidence base of medicine increases, guidelines can provide a useful framework for managing patients with particular diagnoses or symptoms. They can protect patients—particularly those with inadequate health care benefits—from receiving substandard care. Guidelines can also protect conscientious caregivers from inappropriate charges of malpractice and society from the excessive costs associated with the overuse of medical resources. There are, however, caveats associated with clinical practice guidelines since they tend to oversimplify the complexities of medicine. Further-more, groups with differing perspectives may develop divergent recommendations regarding issues as basic as the need for periodic sigmoidoscopy in middle-aged persons. Finally, guidelines do not— and cannot be expected to—account for the uniqueness of each individual and his or her illness. The physician's challenge is to integrate into clinical practice the useful recommendations offered by experts without accepting them blindly or being inappropriately constrained by them.

Medical Decision-Making

Medical decision-making is an important responsibility of the physician and occurs at each stage of the diagnostic and treatment process. It involves the ordering of additional tests, requests for consults, and decisions regarding treatment and prognosis. This process requires an in-depth understanding of the pathophysiology and natural history of

disease. As described above, medical decision-making should be evidence-based so that patients derive the full benefit of the scientific knowledge available to physicians. Formulating a differential diagnosis requires not only a broad knowledge base but also the ability to assess the relative probabilities of various diseases. Application of the scientific method, including hypothesis formation and data collection, is essential to the process of accepting or rejecting a particular diagnosis. Analysis of the differential diagnosis is an iterative process. As new information or test results are acquired, the group of disease processes being considered can be contracted or expanded appropriately.

Reading 2: Principles of Patient Care

Care of the Elderly

The relative proportion of elderly individuals in the populations of developed nations has been growing considerably over the past few decades and will continue to grow. In this regard, the practice of medicine will continue to be greatly influenced by the health care needs of this growing elderly population. The physician must understand and appreciate the decline in physiologic reserve associated with aging; the diminished responses of the elderly to vaccinations such as those against influenza; the different responses of the elderly to common diseases; and disorders that occur commonly with aging, such as depression, dementia, frailty, urinary incontinence, and fractures.

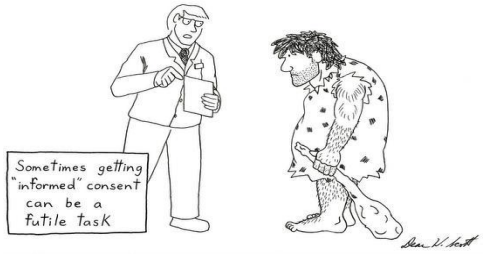
Errors in the Delivery of Health Care

A report from the Institute of Medicine called for an ambitious agenda to reduce medical-error rates and improve patient safety by designing and implementing fundamental changes in health care systems. Adverse drug reactions occur in at least 5% of hospitalized patients, and the incidence increases with use of a large number of drugs. No matter what the clinical situation, it is the responsibility of the physician to use powerful therapeutic measures wisely, with due regard for their beneficial action, potential dangers, and cost. It is also the responsibility of hospitals and health care organizations to develop systems to reduce risk and ensure patient safety. Medication errors can be reduced through the use of ordering systems that eliminate misreading of handwriting. Implementation of infection-control systems, enforcement of hand-washing protocols, and careful oversight of antibiotic use can minimize complications of nosocomial infections.

The Role of the Physician in the Informed Consent of the Patient

The fundamental principles of medical ethics require physicians to act in the patient's best interest and to respect the patient's autonomy. This is particularly relevant to the issue of informed consent. Most patients possess only limited medical knowledge and must rely on their physicians for advice. Physicians must respect their patients' autonomy, fully discussing the alternatives for care and the risks, benefits, and likely consequences of each alternative.

Patients are required to sign a consent form for essentially any diagnostic or therapeutic procedure. In such cases, it is particularly important for the patient to understand clearly the risks and benefits of these procedures; this is the definition of *informed consent*. It is incumbent on the physician to explain the procedures in a clear and understand-able manner and to ascertain that the patient comprehends both the nature of the procedure and the attendant risks and benefits. The dread of the unknown, inherent in hospitalization, can be mitigated by such explanations.



Translation

The Approach to Grave Prognoses and Death

No problem is more distressing than the diagnosis of an incurable disease, particularly when premature death is inevitable. What should the patient and family be told? What measures should be taken to maintain life? What can be done to maintain the quality of life?

Although some would argue otherwise, there is no ironclad rule that the patient must immediately be told "everything," even if the patient is an adult with substantial family responsibilities. How much is told at a given point in time should depend on the individual's ability to deal with the possibility of imminent death; often this capacity grows with time, and, whenever possible, gradual rather than abrupt disclosure is the best strategy. A wise and insightful physician is often guided by an understanding of what a patient wants to know and when he or she wants to know it. The patient's religious beliefs may also be taken into consideration. The patient must be given an opportunity to talk with the physician and ask questions. Patients may find it easier to share their feelings about death with their physician, who is likely to be more objective and less emotional, than with family members. As William Osler wrote, "One thing is certain; it is not for you to don the black cap and, assuming the judicial function, take hope away from any patient." Even when the patient directly inquires, "Am I dying?" the physician must attempt to determine whether this is a re-quest for information or for reassurance. Only open communication between the patient and the physician can resolve this question and guide the physician in what to say and how to say it.

The physician should provide or arrange for emotional, physical, and spiritual support and must be compassionate, unhurried, and open. There is much to be gained by the laying on of hands. Pain should be adequately controlled, human dignity maintained, and isolation from family and close friends avoided. These aspects of care tend to be overlooked in hospitals, where the intrusion of life-sustaining apparati can so easily detract from attention to the whole person and encourage concentration instead on the life-threatening disease, against which the battle will ultimately be lost in any case. In the face of terminal illness, the goal of medicine must shift from *cure* to *care*, in the broadest sense of the term. In offering care to the dying patient, the physician must be prepared to provide information to family members and to deal with their grief and sometimes their feelings of guilt. It is important for the doctor to assure the family that everything possible has been done.

Exercises

1. Comprehension questions: Please answer the following questions:

1. What is evidence based medicine?
2. What is the use of practical guidelines?
3. What are involved in medical decision making?
4. What are the medical problems among the elderly/
5. What is informed consent?
6. How should the physician behave and react to grave prognosis and death?
7. How should the patient's quality of life be sustained?

8. What are the three main contracts of the physician with the society?
9. What are public expectations and physician attitudes and responsibilities?

2. Please fill in the blanks with the following appropriate words

responsibilities insightful maintain emotional consideration imminent incurable distressing premature

No problem is more _____ than the diagnosis of an _____ disease, particularly when _____ death is inevitable. What should the patient and family be told? What measures should be taken to maintain life? What can be done to _____ the quality of life?

Although some would argue otherwise, there is no ironclad rule that the patient must immediately be told "everything," even if the patient is an adult with substantial family _____. How much is told at a given point in time should depend on the individual's ability to deal with the possibility of _____ death; often this capacity grows with time, and, whenever possible, gradual rather than abrupt disclosure is the best strategy. A wise and _____ physician is often guided by an understanding of what a patient wants to know and when he or she wants to know it. The patient's religious beliefs may also be taken into _____. The patient must be given an opportunity to talk with the physician and ask questions. Patients may find it easier to share their feelings about death with their physician, who is likely to be more objective and less _____, than with family members.

3. Please read the following paragraph and draw a diagram for that.

The level of knowledge and sophistication regarding health issues on the part of the general public has grown rapidly over the past few decades. As a result, expectations of the health care system in general and of physicians in particular have risen. Physicians are expected to master rapidly advancing fields (the *science* of medicine) while considering their patients' unique needs (the *art* of medicine). Thus, physicians are held accountable not only for the technical aspects of the care that they provide but also for their patients' satisfaction with the delivery and costs of care.

Unit 2: Immunity

Reading 1

Resistance of the Body to Infection I

Our bodies are exposed continually to bacteria, viruses, fungi, and parasites, all of which occur normally and to varying degrees in the skin, the mouth, the respiratory passageways, the intestinal tract, the lining membranes of the eyes, and even the urinary tract. Many of these infectious agents are capable of causing serious abnormal physiologic function or even death if they invade the deeper tissues. In addition, we are exposed intermittently to other highly infectious bacteria and viruses besides those that are normally present, and these can cause acute lethal diseases such as pneumonia, streptococcal infection, and typhoid fever.

Our bodies have a special system for combating the different infectious and toxic agents. This is comprised of blood leukocytes (white blood cells) and tissue cells derived from leukocytes. These cells work together in two ways to prevent disease: (1) by actually destroying invading bacteria or viruses by phagocytosis, and (2) by forming antibodies and sensitized lymphocytes, one or both of which may destroy or inactivate the invader. This chapter is concerned with the first of these methods,

Leukocytes (White Blood Cells)

The leukocytes, also called white blood cells, are the mobile units of the body's protective system. They are formed partially in the bone marrow (granulocytes and monocytes and a few lymphocytes) and partially in the lymph tissue (lymphocytes and plasma cells). After formation, they are transported in the blood to different parts of the body where they are needed.

The real value of the white blood cells is that most of them are specifically transported to areas of serious infection and inflammation, thereby providing a rapid and potent defense against infectious agents. As we see later, the granulocytes and monocytes have a special ability to "seek out and destroy" a foreign invader.

Resistance of the Body to Infection II: Immunity and Allergy

Innate Immunity

The human body has the ability to resist almost all types of organisms or toxins that tend to damage the tissues and organs. This capability is called immunity. Much of immunity is acquired immunity that does not develop until after the body is first attacked by a bacterium, virus, or toxin, often requiring weeks or months to develop the immunity. An additional portion of immunity results from general processes, rather than from processes directed at specific disease organisms. This is called innate immunity. It includes the following: 1. Phagocytosis of bacteria and other invaders by white blood cells and cells of the tissue macrophage system, 2. Destruction of swallowed organisms by the acid secretions of the stomach and the digestive enzymes. 3. Resistance of the skin to invasion by organisms. 4. Presence in the blood of certain chemical compounds that attach to foreign organisms or toxins and destroy them. Some of these compounds are (1) lysozyme, a mucolytic polysaccharide that attacks bacteria and causes them to dissolute; (2) basic polypeptides, which react with and inactivate certain types of gram-positive bacteria; (3) the complement complex that is described later, a system of about 20 proteins that can be activated in

various ways to destroy bacteria; and (4) natural killer lymphocytes that can recognize and destroy foreign cells, tumor cells, and even some infected cells.

This innate immunity makes the human body resistant to such diseases as some paralytic viral infections of animals, hog cholera, cattle plague, and distemper— a viral disease that kills a large percentage of dogs that become afflicted with it. Conversely, many lower animals are resistant or even immune to many human diseases, such as poliomyelitis, mumps, human cholera, measles, and syphilis, which are very damaging or even lethal to human beings.

Acquired (Adaptive) Immunity

In addition to its generalized innate immunity, the human body has the ability to develop extremely powerful specific immunity against individual invading agents such as lethal bacteria, viruses, toxins, and even foreign tissues from other animals. This is called acquired or adaptive immunity. Acquired immunity is caused by a special immune system that forms antibodies and/or activated lymphocytes that attack and destroy the specific invading organism or toxin. It is with this acquired immunity mechanism and some of its associated reactions— especially the allergies—that this chapter is concerned. Acquired immunity can often bestow extreme protection. For instance, certain toxins, such as the paralytic botulinum toxin or the tetanizing toxin of tetanus, can be protected against in doses as high as 100,000 times the amount that would be lethal without immunity. This is the reason the treatment process known as immunization is so important in protecting human beings against disease and against toxins, as explained in the course of this chapter.

Reading 2

Basic Types of Acquired Immunity

Two basic but closely allied types of acquired immunity occur in the body. In one of these the body develops circulating antibodies, which are globulin molecules in the blood plasma that are capable of attacking the invading agent. This type of immunity is called humoral immunity or B-cell immunity (because B lymphocytes produce the antibodies). The second type of acquired immunity is achieved through the formation of large numbers of activated T lymphocytes that are specifically crafted in the lymph nodes to destroy the foreign agent. This type of immunity is called cell-mediated immunity or T-cell immunity (because the activated lymphocytes are T lymphocytes). We shall see shortly that both the antibodies and the activated lymphocytes are formed in the lymphoid tissues of the body. Let us discuss the initiation of the immune process by antigens.

Both Types of Acquired Immunity Are Initiated by Antigens

Because acquired immunity does not develop until after invasion by a foreign organism or toxin, it is clear that the body must have some mechanism for recognizing this invasion. Each toxin or each type of organism almost always contains one or more specific chemical compounds in its makeup that are different from all other compounds. In general,

these are proteins or large polysaccharides, and it is they that initiate the acquired immunity. These substances are called antigens (antibody generations).

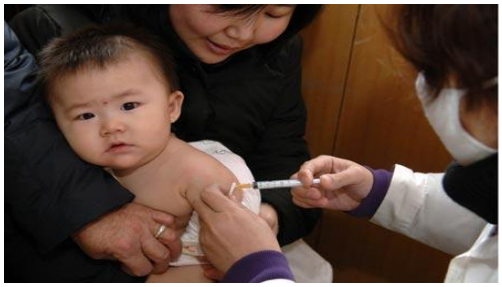
For a substance to be antigenic, it usually must have a high molecular weight, 8000 or greater. Furthermore, the process of antigenicity usually depends on regularly recurring molecular groups, called epitopes, on the surface of the large molecule. This also explains why proteins and large polysaccharides are almost always antigenic, because both of these have this stereochemical characteristic.

How does immunization work?

Information session with community women in Begene, a remote village near the town of Bla, Mali

Immunization works by tricking the body into believing it is experiencing a full-scale invasion by an infectious agent so that the immune system can fortify its defenses. During vaccination, a harmless version of a germ is introduced to the body and the immune system responds by producing antibodies to attack the intruder. Thereafter, a memory of this "invasion" remains so that the immune system can quickly recognize and neutralize disease-causing agents when they appear.

The Chinese performed a version of vaccination called variolation in the 16th century when they discovered they could prevent smallpox by exposing a healthy person to matter from the lesions of an infected person. In 1796, Edward Jenner, an English doctor, performed the first vaccination in Europe when he used a cowpox virus to vaccinate a young boy against the more deadly smallpox virus. (Dr. Jenner called this process vaccination after the Latin word for cow, vacca.)



Today there are several types of vaccines. Some, such as the oral polio vaccine (OPV), are live, "attenuated" vaccines which means the virus has been weakened so that it stimulates antibody production, but does not cause the disease. Others such as the "whole-cell" pertussis vaccine use an inactivated, or killed, virus that still triggers an immune response. Tetanus toxoid (TT), the vaccine that protects mothers and newborns from tetanus, is a detoxified version of the toxin (poison) that causes the disease. A fourth variety of vaccine, such as that for Haemophilus influenzae type b (Hib), uses only the components of the virus or bacteria that provoke an immune response.

Mothers can pass on immunity to their babies across the placenta during the final months of pregnancy. The amount of inherited immunity varies by disease and is an important factor in deciding when a child should be immunized. A mother's antibodies may protect a child from measles for 6 to 12 months. But, in the case of diseases such as pertussis, immunity may last only for a few weeks. Tetanus is one example where inherited immunity is critical and the mother must

be immunized to offer protection to her newborn.

For many diseases, immunity is built up over several doses of vaccine. The World Health Organization (WHO) recommends that the first polio vaccine be given at birth, along with the vaccine for childhood tuberculosis (BCG). In countries where transmission of hepatitis B from mother to child is common, these infants should be immunized against the disease at birth.

The remaining doses of polio vaccine and the combination diphtheria, pertussis, tetanus vaccine (DPT) should be given three times before the age of one: at six weeks, 10 weeks and 14 weeks. Due to inherited immunity, measles vaccines are typically given at nine months. Yellow fever is also given at this time for children in high-risk regions.

The more children in a community that are vaccinated, the less likely it is that any children, even those who have not been immunized, will get sick because there are fewer hosts for the infectious agents. This is referred to as “herd” immunity and it is particularly vital with extremely contagious diseases such as measles, where immunization of 90 to 95 per cent of infants is needed to protect a community from measles. However, this is not true for all diseases, such as tetanus, therefore an individual’s vaccination status is important, not just group immunity.

Unit 3: Public Health: Communicable Diseases

Reading 1: AIDS

AIDS

Here the discussion will be limited to AIDS in the developing world. Lessons learned in tackling AIDS in resource-constrained settings are highly relevant to discussions of other chronic diseases, including noncommunicable diseases, for which effective therapies have been developed. Several of these lessons are highlighted below.

In the United States, the availability of highly active antiretroviral therapy (ART) for AIDS has transformed this disease from an inescapably fatal destruction of cell-mediated immunity into a manageable chronic illness. In developing countries, treatment has been offered more broadly only since 2003, and only in the fall of 2008 did the number of patients receiving treatment exceed 40% of the number who need it. (It remains to be seen how many of these fortunate few are receiving ART regularly and with the requisite social support.) Before 2003, many arguments were raised to justify not moving forward rapidly with ART programs for people living with HIV/AIDS in resource-limited settings. The standard litany included the price of therapy compared with the poverty of the patient, the complexity of the intervention, the lack of infrastructure for laboratory monitoring, and the lack of trained health care providers. Narrow cost-effectiveness arguments that created false dichotomies—prevention *or* treatment rather than both—too often went unchallenged. The greatest obstacle at the time was the ambivalence, if not outright silence, of political leaders and experts in public health. The cumulative effect of these factors was to condemn to death tens of millions of poor people in developing countries who had become ill as a result of HIV infection.

The inequity between rich and poor countries in access to HIV treatment has given rise to widespread moral indignation. In several middle-income countries, including Brazil, visionary programs have bridged the access gap. Other innovative projects pioneered by international nongovernmental organizations (NGOs) in diverse settings have clearly established that a very simple approach to ART that is based on intensive community engagement and support can achieve remarkable results. In 2000, the United Nations Accelerating Access Initiative finally brought the research-based and generic pharmaceutical industries into play, and prices of AIDS drugs have fallen significantly. At the same time, fixed-dose combination drugs that are easier to administer have become more widely available.

How to Recognize HIV Symptoms

HIV (human immunodeficiency virus) is the virus that causes AIDS. HIV attacks the immune system, destroying a type of white blood cell that helps the body fight off infection and disease. Testing is the only sure way to determine if you have HIV. There are symptoms to look for that could be a warning that you have an infection.

Method 1 of 3: Spotting Early Symptoms

Determine if you are experiencing acute fatigue with no explainable cause.

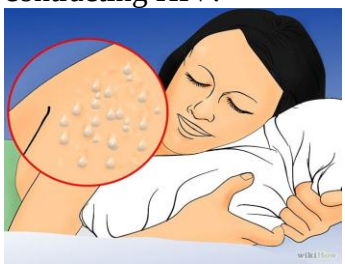
Fatigue can be the sign of many different illnesses, but it's a symptom many people with HIV experience. This symptom

shouldn't cause great alarm if it's the only one you're feeling, but it's something to look into further.

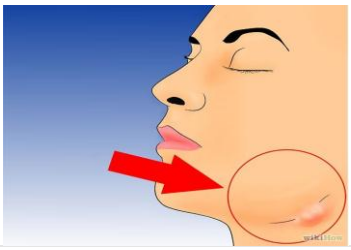
- Acute fatigue isn't the same as simply feeling sleepy. Do you feel tired all the time, even after a good night's sleep? Do you find yourself taking more afternoon naps than usual, and avoiding strenuous activities because you feel low energy? This type of fatigue is cause for concern.
- If this symptom persists over a few weeks or months' time, be sure to get tested to rule out HIV.

Be on the lookout for a fever or excessive night sweats.

These symptoms commonly occur during the early stages of an HIV infection, during what is called the primary or acute HIV infection stage. Again, many people don't have these symptoms, but those who do usually experience them 2 to 4 weeks after contracting HIV.



- Fever and night sweats are also symptoms of the flu and the common cold. If it's flu or cold season, that might be what you're experiencing.
- Chills, muscle aches, sore throat, and headache, which are also symptoms of the flu and cold, can also be signs of an early HIV infection.

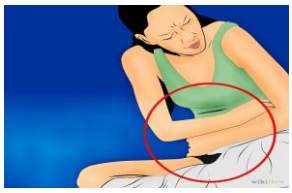


Check for swollen glands in the neck, armpits, or groin.

The lymph nodes swell in reaction to bodily infections. This doesn't happen to everyone who has primary HIV, but among those who have symptoms, it's a common one.

- The lymph nodes in the nick tend to swell more than those in the armpits or groin with an HIV infection.
- Lymph nodes can swell as a result of many other types of infections, such as the cold or a flu, so further investigation is necessary to determine the cause.

Recognizing Advanced Symptoms

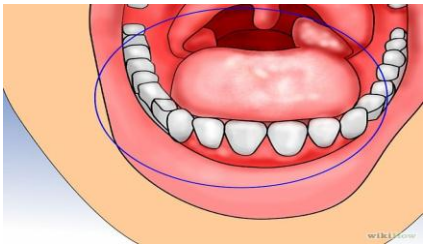


Note instances of nausea, vomiting and diarrhea.

These symptoms, which are commonly associated with the flu, can also indicate an early HIV infection. Get tested if these symptoms persist.

Pay attention to mouth and genital ulcers.

If you see a mouth ulcer appear along with the other symptoms noted, especially if you don't commonly get mouth ulcers, it may be a sign of primary HIV infection. Genital ulcers are also an indication that HIV may be present.



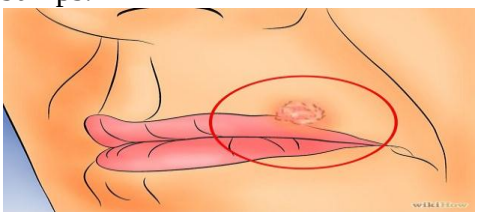
Don't dismiss a dry cough.

This symptom occurs in the later stages of HIV, sometimes many years after the virus has been contracted and been latent in the body. This seemingly innocuous symptom is easy to ignore at first, especially if it occurs during allergy season or during cough and cold season. If you have a dry cough you just can't seem to kick by taking allergy medications or using an inhaler, it may be a symptom of HIV.

Look into irregular spots (red, brown, pink, or purplish in color) on the skin.

People in the later stages of HIV often get rashes on their skin, especially on the face and torso. These can also be present on the inside of the mouth and nose. It's a sign that the HIV is developing into AIDS.[5]

- Flaky, red skin is also a sign of later stage HIV. The spots may also look like boils or bumps.



- A skin rash usually doesn't accompany the flu or a cold, so if you have one at the same time as other symptoms, see a doctor right away.

Pay attention if you get pneumonia.

Pneumonia often affects people whose immune systems aren't working properly for other reasons. People with later-stage HIV are prone to getting pneumonia from a germ that wouldn't normally cause such a severe reaction.

Check for yeast infections, especially in the mouth.

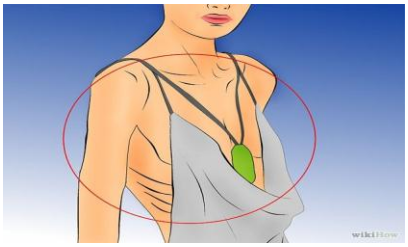
Later-stage HIV patients commonly get a yeast infection in the mouth, called thrush. The condition looks like white spots or other unusual spots on the tongue and inside of the mouth. This is a warning sign that immune system isn't effectively fighting off infection.

Examine your nails for signs of fungus.

Nails that are yellow or brown, and that are cracked or chipped, are common among later-stage HIV patients. The nails become more susceptible to fungus, which the body is able to fight off under normal conditions.

Determine whether you're experiencing rapid weight loss with no known cause.

In the early stages of HIV, this could be caused by excessive diarrhea; in later stages, it's known as "wasting," and is a strong bodily reaction to the presence of HIV in the system.



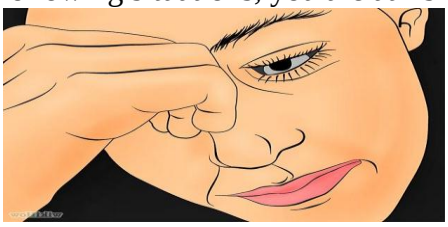
Understanding HIV

Be aware of issues with memory loss, depression, or other neurological afflictions.

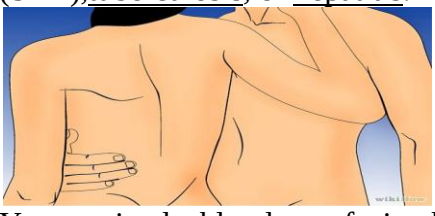
HIV affects the cognitive function of the brain in later stages. These symptoms are serious and should be looked into no matter what.

Know if you are at risk.

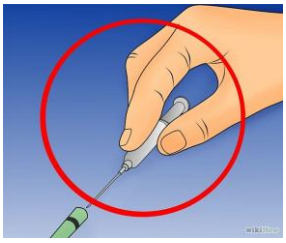
There are several different circumstances that can place you at risk of contracting HIV. If you've experienced one of the following situations, you are at risk:[6]



- You've had unprotected anal, vaginal, or oral sex.
- You've shared needles or syringes.
- You've been diagnosed or treated for a sexually transmitted disease (STD),tuberculosis, or hepatitis.

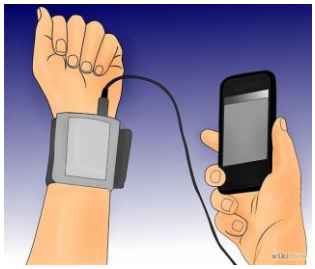


- You received a blood transfusion between 1978 and 1985, the years before safety precautions were in place to prevent tainted blood from being used in transfusions.



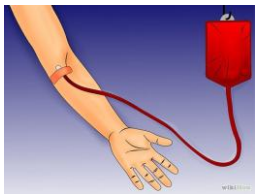
Don't wait for symptoms to occur to get tested.

Many people HIV don't know they have it. The virus can be carried in your body for over ten years before symptoms begin to occur. If you have reason to think you may have contracted HIV, don't let a lack of symptoms stop you from getting tested. It's best to know as soon as possible.



Get tested for HIV.

This is the most accurate measure in determining if you have HIV. Contact a local health clinic, the Red Cross, your doctor's office, or another local resource to find out where to get tested. Go to the website aids.gov for a listing of testing locations.



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- Testing is easy, affordable, and reliable (in the majority of cases). The most common test is done through drawing a blood

sample. There are also tests that use oral fluids (not saliva) and urine. There are even tests you can take at home. If you do not have a regular physician who can provide testing, contact your local Health Department.

- If you are tested for HIV, do not let fear prevent you from obtaining your test results. Knowing if you are infected, or not, brings about change in your lifestyle and your way of thinking

Reading 2

Tuberculosis and AIDS as Chronic Diseases: Lessons Learned

Strategies effective against MDR TB have implications for the management of drug-resistant HIV infection and even drug-resistant malaria, which, through repeated infections and a lack of effective therapy, has become a chronic disease in parts of Africa. Indeed, examining AIDS and TB together as chronic diseases allows us to draw a number of conclusions, many of them pertinent to global health in general.

First, charging fees for AIDS prevention and care will pose insurmountable problems for people living in poverty, many of whom will always be unable to pay even modest amounts for services or medications. Like efforts to battle airborne TB, such services might best be seen as a public good for public health. Initially, this approach will re-quire sustained donor contributions, but many African countries have recently set targets for increased national investments in health—a pledge that could render ambitious programs sustainable in the long run. Meanwhile, as local investments increase, the price of AIDS care is decreasing. The development of generic medications means that ART can now cost <$0.50 (U.S.) per day, and costs continue to decrease to affordable levels for public health bodies in developing countries.

Second, the effective scale-up of pilot projects will require the strengthening and sometimes rebuilding of health care systems, including those charged with delivering primary care. In the past, the lack of health care infrastructure has been cited as a barrier to providing ART in the world's poorest regions; however, AIDS resources, which are at last considerable, may be marshaled to rebuild public health systems in sub-Saharan Africa and other HIV-burdened regions—precisely the settings in which TB is resurgent.

Third, a lack of trained health care personnel, most notably doctors, is invoked as a reason for the failure to treat AIDS in poor countries. The lack is real, and the "brain drain," which is discussed below, continues. However, one reason doctors leave Africa is that they lack the tools to practice their trade there. AIDS funding provides an opportunity not only to recruit physicians and nurses to underserved regions but also to train community health workers to supervise care for AIDS and many other diseases within their home villages and neighborhoods. Such training should be undertaken even in places where physicians are abundant, since community-based, closely supervised care represents the highest standard of care for chronic disease, whether in the First World or the Third.

Fourth, extreme poverty makes it difficult for many patients to comply with therapy for chronic diseases, whether communicable or not. Indeed, poverty in

its many dimensions is far and away the greatest barrier to the scale-up of treatment and prevention programs. It is possible to remove many of the social and economic barriers to adherence, but only with what are sometimes termed "wrap-around services": food supplements for the hungry, help with transportation to clinics, child care, and housing. In many rural regions of Africa, hunger is the major coexisting condition in patients with AIDS or TB, and these consumptive diseases cannot be treated effectively without adequate caloric intake.

Finally, there is a need for a renewed basic-science commitment to the discovery and development of vaccines; of more reliable, less expensive diagnostic tools; and of new classes of therapeutic agents. This need applies not only to the three leading infectious killers—against none of which an effective vaccine exists—but also to many other neglected diseases of poverty.

Translation

Malaria

We turn now to the world's third largest infectious killer, which has taken its greatest toll among children, especially African children, living in poverty. The Cost of Malaria Malaria's human toll is enormous. An estimated 250 million people suffer from malarial disease each year, and the disease annually kills between 1 million and 2.5 million people, mostly pregnant women and children under the age of 5. The poor disproportionately suffer the consequences of malaria: 58% of malaria deaths occur in the poorest 20% of the world's population, and 90% are registered in sub-Saharan Africa. The differential magnitude of this mortality burden is greater than that associated with any other disease. Likewise, the morbidity differential is greater for malaria than for diseases caused by other pathogens, as documented in a study from Zambia that revealed a 40% greater prevalence of parasitemia among children under 5 in the poorest quintile than in the richest. Despite suffering the greatest consequences of malaria, the poor are precisely those least able to access effective prevention and treatment tools. Economists describe the complex interactions between malaria and poverty from an opposite but complementary perspective: they decombination antimalarial therapy, and indoor residual spraying. ITNs are an efficacious and cost-effective public health intervention.

A meta-analysis of controlled trials indicates that malaria incidence is reduced by 50% among persons who sleep under ITNs compared with that among those who do not use nets at all. Even untreated nets reduce malaria incidence by one-quarter. On an individual level, the utility of ITNs extends beyond protection from malaria. Several studies suggest that all-cause mortality is reduced among children under 5 to a greater degree than can be attributed to the reduction in malarial disease alone. Morbidity (specifically that due to anemia) predisposing children to diarrheal and respiratory illnesses and pregnant women to the delivery of low-birth-weight infants is also reduced in populations using ITNs. In some areas, ITNs offer a supplemental benefit by preventing transmission of lymphatic filariasis, cutaneous leishmaniasis, Chagas' disease, and tick-borne relapsing fever. At the community level, investigators suggest that the use of an ITN in just one household may reduce the number of mosquito bites in households up to several hundred meters away. The cost of ITNs per DALY saved is estimated at $10–$38 (U.S.), which qualifies ITNs as a "very efficient use of resources and [a] good candidate for public subsidy."

Unit 4: Public Health: Noncommunicable Diseases

Reading 1

Chronic Noncommunicable Diseases

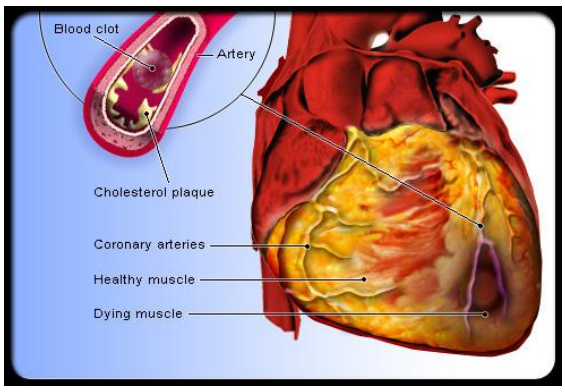
While the burden of communicable diseases—especially HIV infection, tuberculosis, and malaria—still accounts for the majority of deaths in resource-poor regions such as sub-Saharan Africa, close to 60% of all deaths worldwide in 2005 were due to chronic noncommunicable diseases (NCDs). Moreover, 80% of deaths attributable to NCDs occurred in low- and middle-income countries, where 85% of the global population lives. In 2005, 8.5 million people in the world died of an NCD before their 60th birthday—a figure exceeding the to-tal number of deaths due to AIDS, TB, and malaria combined. By 2020, NCDs will account for 80% of the GBD and for 7 of every 10 deaths in developing countries. The recent rise in resources for and attention to communicable diseases is both welcome and long overdue, but developing countries are already carrying a "double burden" of communicable and noncommunicable diseases.

Cardiovascular Disease

Unlike TB, HIV infection, and malaria—dis-eases caused by single pathogens that damage multiple organs—cardio-vascular diseases reflect injury to a single organ system downstream of a variety of insults. The burden of chronic cardiovascular disease in low-income countries represents one consequence of decades of health system neglect; furthermore, cardiovascular research and investment have long focused on the ischemic conditions that are increasingly common in high- and middle-income countries. Meanwhile, despite awareness of its health impact during the early twentieth century, cardiovascular damage in response to infection and malnutrition has fallen out of view until recently.

The perception of cardiovascular diseases as a problem of elderly populations in middle- and high-income countries has contributed to their neglect by global health institutions. Even in Eastern Europe and Central Asia, where the collapse of the Soviet Union was followed by a catastrophic surge in cardiovascular disease deaths (mortality rates from ischemic heart disease nearly doubled between 1991 and 1994 in Russia, for example), the modest flows of overseas development assistance to the health sector focused on the communicable causes that accounted for <1 in 20 excess deaths during this period.

Predictions of an imminent rise in the share of deaths and disabilities due to NCDs in developing countries have led to calls for preventive policies to restrict tobacco use, improve diet, and increase exercise along-side the prescription of multidrug regimens for persons with high levels of vascular risk. Although this agenda could do much to prevent pandemic NCD, it will do little to help those with established heart disease stemming from non-atherogenic pathologies.



The epidemiology of heart failure reflects inequalities in risk factor prevalence and treatment. Heart failure as a

consequence of pericardial, myocardial, endocardial, or valvular injury accounts for as many as 1 in 10 admissions to hospitals around the world. Countries have reported a remarkably similar burden of this condition at the health system level since the 1950s, but the causes of heart failure and the age of the people affected vary with resources and ecology. In populations with a high human-development index, coronary artery disease and hypertension among the elderly account for most cases of heart failure. Among the world's poorest billion people, however, heart failure reflects poverty-driven exposure of children and young adults to rheumatogenic strains of streptococci and cardiotropic microorganisms (e.g., HIV, *Trypanoso-ma cruzi*, enteroviruses, *M. tuberculosis*), untreated high blood pressure, and nutrient deficiencies. The mechanisms of other causes of heart failure common in these populations—such as idiopathic dilated cardiomyopathy, peripartum cardiomyopathy, and endomyocardial fibrosis—remain unclear.

Of the 2.3 million annual cases of pediatric rheumatic heart disease, nearly half occur in sub-Saharan Africa. This disease leads to more than 33,000 cases of endocarditis, 252,000 strokes, and 680,000 deaths per year—almost all in developing countries. Researchers in Ethiopia have reported annual death rates as high as 12.5% in rural areas. In part be-cause the prevention of rheumatic heart disease has not advanced since the disappearance of this disease in wealthy countries, no part of sub-Saharan Africa has yet eradicated rheumatic heart disease despite examples of success in Costa Rica, Cuba, and some Caribbean nations.

Strategies to eliminate rheumatic heart disease may depend on active case-finding confirmed by echocardiography among high-risk groups as well as efforts to extend access to surgical interventions among children with advanced valvular damage. Partnerships between established surgical programs and areas with limited or nonexistent facilities may help develop capacity and provide care to patients who would otherwise suffer an early and painful death. A long-term goal is the establishment of regional centers of excellence equipped to provide consistent, accessible, high-quality services.

In stark contrast to the extraordinary lengths to which patients in wealthy countries will go to treat ischemic cardiomyopathy, young patients with nonischemic cardiomyopathies in resource-poor settings have received little attention. These conditions account for as many as 25–30% of admissions for heart failure in sub-Saharan Africa and include poorly understood entities such as peripartum cardiomyopathy (which has an incidence in rural Haiti of 1 per 300 live births) and HIV cardiomyopathy. Multidrug regimens that include heart failure beta-blockers, ACE inhibitors, and other neurohormonal antagonists can dramatically reduce mortality risk and improve quality of life for these patients. Lessons learned in the scale-up of chronic care for HIV infection and TB may be illustrative as progress is made in establishing means to deliver cardiac therapies over a background of careful fluid management with diuretic drugs.

Because systemic investigation of the causes of stroke and heart failure in sub-Saharan Africa has begun only recently, little is known about the impact of elevated blood pressure in this portion of the continent. Modestly elevated blood pressure in the absence of tobacco use in populations with low rates of obesity may confer little risk of adverse events in the short run. In contrast, persistently elevated blood pressure above 180/110 goes largely undetected, untreated, and uncontrolled in this set-ting. In the Framingham cohort of men 45–74 years old, the prevalence of blood pressures above 210/120 declined

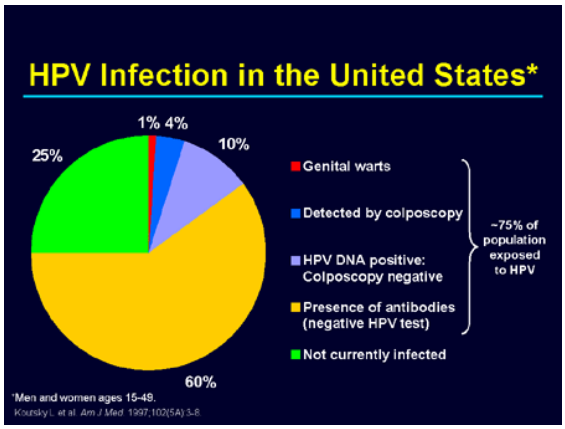
from 1.8% in the 1950s to 0.1% in the 1990s with the introduction of effective antihypertensive agents. While debate continues about appropriate screening strategies and treatment thresholds, rural health centers staffed by nonphysicians must quickly gain access to essential antihypertensive medications.

In 1960, Paul Dudley White and colleagues reported on the prevalence of cardiovascular disease in the region near the Albert Schweitzer Hospital in Lambaréné, Gabon. Although the group found little evidence of myocardial infarction, they concluded that "*the high prevalence of mitral stenosis* [sic] is astonishing. We believe strongly that it is a duty to help bring to these sufferers the benefits of better penicillin prophylaxis and of cardiac surgery when indicated. The same responsibility exists for those with correctable congenital cardiovascular defects."[2] Leaders from tertiary centers in sub-Saharan Africa and elsewhere have continued to call for prevention and treatment of the cardiovascular conditions of the poor. The reconstruction of health services in response to pandemic infectious disease offers an opportunity to identify and treat patients with organ damage and to undertake the prevention of cardiovascular and other chronic conditions of poverty.

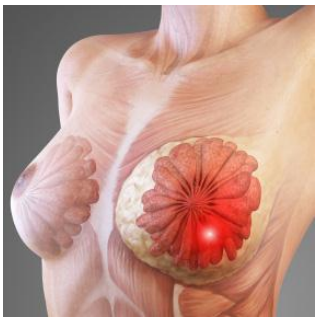
Reading 2

Cancer

Low- and middle-income countries accounted for 53% and 56%, respectively, of the 10 million cases and 7 million deaths due to cancer in 2000. By 2020, the total number of new cancer cases will rise by 29% in developed countries and by 73% in developing countries.



Also by 2020, overall mortality from cancer will increase by 104%, and the increase will be fivefold higher in developing than in developed countries. "Western" lifestyle changes will be responsible for the in-creased incidence of cancers of the breast, colon, and prostate, but historic realities, sociocultural and behavioral factors, genetics, and poverty itself will also have a profound impact on cancer-related mortality and morbidity. While infectious causes are responsible for <10% of cancers in developed countries, they account for 25% of all malignancies in low- and middle-income countries. Infectious causes of cancer such as human papillomavirus (cervical cancer), hepatitis B virus (liver cancer), and *Helicobacter pylori* (stomach cancer) will continue to have a much larger impact in developing countries. Environmental and dietary factors, such as indoor air pollution and high-salt diets, also help account for increased rates of certain cancers (e.g., lung and stomach cancers). Tobacco use (both smoking and chewing) is the most important source of increased mortality from lung and oral cancers. In contrast to decreasing tobacco use in many developed countries, the number of smokers is growing in developing countries, especially among women and young people.



For many reasons, outcomes of malignancies are far worse in developing countries than in developed nations. Overstretched health systems in poor countries simply are not capable of early detection; 80% of patients already have incurable malignancies at diagnosis. Treatment of cancers is available for only a very small number of mostly wealthy citizens in the majority of poor countries, and, even when treatment is available, the range and quality of services are often substandard.

Diabetes

The International Diabetes Federation reports that the number of diabetics in the world is expected to increase from 194 mil-lion in 2003 to 330 million by 2030, when 3 of every 4 sufferers will live in developing countries. Because diabetics are far more frequently under the age of 65 in developing nations, the complications of micro-and macrovascular disease take a far greater toll. In 2005, an estimated 1.1 million people died of diabetes-related illnesses, and >80% of these deaths occurred in low- and middle-income countries.

Obesity and Tobacco Use

In 2004, the WHO released its Global Strategy on Diet, Physical Activity and Health, which focused on the population-wide promotion of healthy diet and regular physical activity in an effort to reduce the growing global problem of overweight and obesity. Passing this strategy at the World Health Assembly proved difficult because of strong opposition from the food industry and from a number of WHO member states, including the United States. While globalization has had many positive effects, one negative aspect has been the growth in both developed and developing countries of well-financed lobbies that have aggressively promoted unhealthy dietary changes and increased consumption of alcohol and tobacco. Foreign direct investment in tobacco, beverage, and food products in developing countries reached $327 million in 2002—a figure nearly five times greater than the amount spent during that year to address NCDs by bi-lateral funding agencies, the WHO, and the World Bank combined.

The Three Pillars of Prevention

The WHO estimates that 80% of all cases of cardiovascular disease and type 2 diabetes as well as 40% of all cancers can be prevented through the three pillars of healthy diet, physical activity, and avoidance of tobacco. While there is some evidence that population-based measures can have some impact on these behaviors, it is sobering to note that increasing obesity levels have not been successfully reversed in any population, including those of high-income countries with robust diet industries. Nonetheless, in Mauritius, for example, a single policy measure that changed the type of cooking oil available to the population led to a fall in mean serum cholesterol levels. Tobacco avoidance may be the most important and most difficult behavioral modification of all. In the twentieth century, 100 million people died worldwide of tobacco-related diseases; it is projected that >1 billion people will die of these diseases in the twenty-first century, with the vast majority of these deaths in developing countries. Today, 80% of the world's 1.2 billion smokers live in low-and middle-income countries, and, while tobacco consumption

is falling in most developed countries, it continues to rise at a rate of ~3.4% per year in developing countries. The WHO's Framework Convention on Tobacco Control was a major advance, committing all of its signatories to a set of policy measures that have been shown to reduce tobacco consumption. However, most developing countries have continued to take a passive approach to the control of smoking.

Translation

Environmental Health

In a recent publication that examined how specific diseases and inju-ries are affected by environmental risk, the WHO determined that ~24% of the total GBD, one-third of the GBD among children, and 23% of all deaths are due to modifiable environmental factors. Many of these factors lead to deaths from infectious diseases; others lead to deaths from malignancies. Increasingly, etiology and nosology are difficult to parse. As much as 94% of diarrheal disease, which is linked to unsafe drinking water and poor sanitation, can be attributed to environmental factors. Risk factors such as indoor air pollution due to use of solid fuels, exposure to second-hand tobacco smoke, and out-door air pollution account for 20% of lower respiratory infections in developed countries and for as many as 42% of such infections in developing countries. Various forms of unintentional injury and malaria top the list of health problems to which environmental factors contribute. Some 4 million children die every year from causes related to unhealthy environments, and the number of infant deaths due to environmental factors in developing countries is 12 times that in developed countries.

Mental Health

The WHO reports that some 450 million people worldwide are affect-ed by mental, neurologic, or behavioral problems at any given time and that ~873,000 people die by suicide every year. Major depression is the leading cause of lost DALYs in the world today. One in four patients visiting a health service has at least one mental, neurologic, or behavioral disorder, but most of these disorders are neither diagnosed nor treated. Most low- and middle-income countries devote <1% of their already-paltry health expenditures to mental health.

Increasingly effective therapies exist for many of the major causes of mental disorder. Effective treatments for many neurologic diseases, including seizure disorders, have long been available. One of the greatest barriers to delivery of such therapies is the paucity of skilled personnel. Most sub-Saharan African countries have only a handful of psychiatrists, for example; most of them practice in cities and are unavailable within the public sector or to patients living in poverty. Of the few patients who are fortunate enough to see a psychiatrist or neurologist, fewer still are able to adhere to treatment regimens: several surveys of already-diagnosed patients ostensibly receiving daily therapy have revealed that, among the poor, few can take their medications as prescribed. The same barriers that prevent the poor from having re-liable access to insulin or ART also prevent them from benefiting from antidepressant, antipsychotic, and antiepileptic agents. To alleviate this problem, some authorities are proposing the training of health workers to provide community-based adherence support, counseling services, and referrals for patients in need of mental health services.

World Mental Health: Problems and Priorities in Low-Income Countries offers a comprehensive analysis of the burden of mental, behavioral, and social problems in low-income countries and relates the mental health consequences of social forces such as violence, dislocation, poverty, and the disenfranchisement of women to current economic, political, and environmental concerns.

Unit 5: Diseases of the Respiratory System

Reading 1: Approach to the Patient with Disease of the Respiratory System

*f*rom Harrison's Principles of Internal Medicine

Introduction

The majority of diseases of the respiratory system fall into one of three major categories: (1) obstructive lung diseases; (2) restrictive disorders; and (3) abnormalities of the vasculature. Obstructive lung diseases are most common and primarily include disorders of the airways such as asthma, chronic obstructive pulmonary disease (COPD), bronchiectasis, and bronchiolitis. Diseases resulting in restrictive pathophysiology include parenchymal lung diseases, abnormalities of the chest wall and pleura, as well as neuromuscular disease. Disorders of the pulmonary vasculature are not always recognized and include pulmonary embolism, pulmonary hypertension, and pulmonary venoocclusive disease. Although many specific diseases fall into these major categories, both infective and neoplastic processes can affect the respiratory system and may result in myriad pathologic findings, including obstruction, restriction, and pulmonary vascular disease

The majority of respiratory diseases present with abnormal gas exchange. Disorders can also be grouped into the categories of gas exchange abnormalities, including hypoxemic, hypercarbic, or combined impairment. Importantly, many diseases of the lung do not manifest gas exchange abnormalities.

As with the evaluation of most patients, the approach to a patient with disease of the respiratory system begins with a thorough history. A focused physical examination is helpful in further categorizing the specific pathophysiology. Many patients will subsequently undergo pulmonary function testing, chest imaging, blood and sputum analysis, a variety of serologic or microbiologic studies, and diagnostic procedures, such as bronchoscopy. This step-wise approach is discussed in detail below.

Dyspnea and Cough

The cardinal symptoms of respiratory disease are dyspnea and cough. Dyspnea can result from many causes, some of which are not predominantly caused by lung pathology. The words a patient uses to describe breathlessness or shortness of breath can suggest certain etiologies of the dyspnea. Patients with obstructive lung disease often complain of "chest tightness" or "inability to get a deep breath," whereas patients with congestive heart failure more commonly report "air hunger" or a sense of suffocation.

The tempo of onset and duration of a patient's dyspnea are helpful in determining the etiology. Acute shortness of breath is usually associated with sudden physiological changes, such as laryngeal edema, bronchospasm, myocardial infarction, pulmonary embolism, or pneumothorax. Patients with underlying lung disease commonly have progressive shortness of breath or episodic dyspnea. Patients with COPD and idiopathic pulmonary fibrosis (IPF) have a gradual progression of dyspnea on exertion, punctuated by acute exacerbations of shortness of breath. In contrast, most

asthmatics have normal breathing the majority of the time and have recurrent episodes of dyspnea usually associated with specific triggers, such as an upper respiratory tract infection or exposure to allergens.

Specific questioning should focus on factors that incite the dyspnea, as well as any intervention that helps resolve the patient's shortness of breath. Of the obstructive lung diseases, asthma is most likely to have specific triggers related to sudden onset of dyspnea, although this can also be true of COPD. Many patients with lung disease report dyspnea on exertion. It is useful to determine the degree of activity that results in shortness of breath as it gives the clinician a gauge of the patient's degree of disability. Many patients adapt their level of activity to accommodate progressive limitation. For this reason it is important, particularly in older patients, to delineate the activities in which they engage and how they have changed over time. Dyspnea on exertion is often an early symptom of underlying lung or heart disease and warrants a thorough evaluation.

Cough is the other common presenting symptom that generally indicates disease of the respiratory system. The clinician should inquire about the duration of the cough, whether or not it associated with sputum production, and any specific triggers that induce it. Acute cough productive of phlegm is often a symptom of infection of the respiratory system, including processes affecting the upper airway (e.g., sinusitis, tracheitis) as well as the lower airways (e.g., bronchitis, bronchiectasis) and lung parenchyma (e.g., pneumonia). Both the quantity and quality of the sputum, including whether it is blood-streaked or frankly bloody, should be determined. Hemoptysis warrants an evaluation as delineated in Chap. 34.

Chronic cough (defined as persisting for more than 8 weeks) is commonly associated with obstructive lung diseases, particularly asthma and chronic bronchitis, as well as "nonrespiratory" diseases, such as gastroesophageal reflux (GERD) and postnasal drip. Diffuse parenchymal lung diseases, including idiopathic pulmonary fibrosis, frequently present with a persistent, nonproductive cough. As with dyspnea, all causes of cough are not respiratory in origin, and assessment should consider a broad differential, including cardiac and gastrointestinal diseases as well as psychogenic causes.

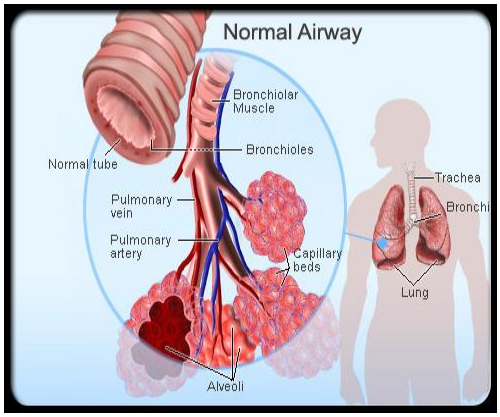
Reading 2

Asthma

Asthma is a syndrome characterized by airflow obstruction that varies markedly, both spontaneously and with treatment. Asthmatics harbor a special type of inflammation in the airways that makes them more responsive than nonasthmatics to a wide range of triggers, leading to excessive narrowing with consequent reduced airflow and symptomatic wheezing and dyspnea. Narrowing of the airways is usually reversible, but in some patients with chronic asthma there may be an element of irreversible airflow obstruction. The increasing global prevalence of asthma, the large burden it now imposes on patients, and the high health care costs have led to extensive research into its mechanisms and treatment.

Prevalence

Asthma is one of the most common chronic diseases globally and currently affects ~300 million people. The prevalence of asthma has risen in affluent countries over the last 30 years but now appears to have stabilized, with ~10–12% of adults and 15% of children affected by the disease. In developing countries where the prevalence of asthma had been much lower, there is a rising incidence that appears to be associated with increased urbanization. The prevalence of atopy and other allergic diseases has also increased over the same time, suggesting that the reasons for the increase are likely to be systemic rather than confined to the lungs. This epidemiologic observation suggests that there is a maximum number of individuals in the community who are liable to be affected by asthma, likely by genetic predisposition. Most patients with asthma in affluent countries are atopic, with allergic sensitization to the house dust mite Dermatophagoides pteronyssinus and other environmental allergens.



Asthma is both common and frequently complicated by the effects of smoking on the lungs; hence, it is difficult to be certain about the natural history of the disease in adults. Asthma can present at any age with a peak age of 3 years. In childhood, twice as many males as females are asthmatic, but by adulthood the sex ratio has equalized. The commonly held belief that children "grow out of their asthma" is justified to some extent. Long-term studies that have followed children until they reach the age of 40 years suggest that many with asthma become asymptomatic during adolescence but that asthma returns in some during adult life, particularly in children with persistent symptoms and severe asthma. Adults with asthma, including those with onset during adulthood rarely become permanently asymptomatic. The severity of asthma does not vary significantly within a given patient; those with mild asthma rarely progress to more severe disease, whereas those with severe asthma usually have severe disease at the onset.

Deaths from asthma are uncommon and have been steadily declining in many affluent countries over the last decade. A rise in asthma mortality seen in several countries during the 1960s was associated with increased use of short-acting β2-adrenergic agonists (as rescue therapy), but there is now compelling evidence that the more widespread use of inhaled corticosteroids (ICSs) in patients with persistent asthma is responsible for the decrease in mortality in recent years. Major risk factors for asthma deaths are poorly controlled disease with frequent use of bronchodilator inhalers, lack of corticosteroid therapy, and previous admissions to the hospital with near-fatal asthma.

It has proved difficult to agree on a definition of asthma, but there is good agreement on the description of the clinical

syndrome and disease pathology. Until the etiologic mechanisms of the disease are better understood, it will be difficult to provide an accurate definition.

Translation

Infections

Although viral infections are common as triggers of asthma exacerbations, it is uncertain whether they play a role in etiology. There is some association between respiratory syncytial virus infection in infancy and the development of asthma, but the specific pathogenesis is difficult to elucidate, as this infection is very common in children. More recently, atypical bacteria such as Mycoplasma and Chlamydia have been implicated in the mechanism of severe asthma, but thus far evidence of a true association is not very convincing.

Risk Factors and Triggers Involved in Asthma

Endogenous Factors	Environmental Factors
Genetic predisposition Atopy Airway hyperresponsiveness Gender Ethnicity?	Indoor allergens Outdoor allergens Occupational sensitizers Passive smoking Respiratory infections Obesity? Early viral infections?

Triggers

Allergens

Upper respiratory tract viral infections
Exercise and hyperventilation
Cold air
Sulfur dioxide
Drugs (β blockers, aspirin)
Stress

It is likely that environmental factors in early life determine which atopic individuals become asthmatic. The increasing prevalence of asthma, particularly in developing countries, over the last few decades also indicates the importance of environmental mechanisms interacting with a genetic predisposition.

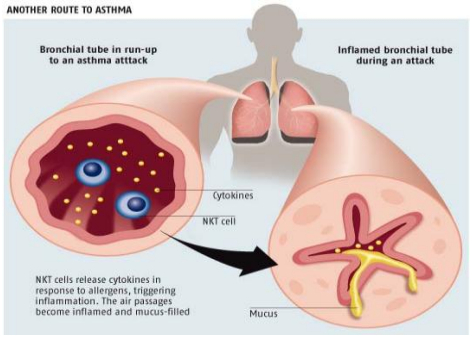
Asthma Triggers

Hygiene Hypothesis

The observation that allergic sensitization and asthma were less common in children with older siblings first suggested that lower levels of infection may be a factor in affluent societies that increase the risks of asthma. This "hygiene hypothesis" proposes that lack of infections in early childhood preserves the T_H2 cell bias at birth, whereas exposure to infections and endotoxin results in a shift toward a predominant protective T_H1 response. Children brought up on farms who are exposed to a high level of endotoxin are less likely to develop allergic sensitization than children raised on dairy farms. Intestinal parasite infection may also be associated with a reduced risk of asthma. While there is considerable epidemiologic support for the hygiene hypothesis, it cannot account for the parallel increase in T_H1-driven diseases, such as diabetes mellitus, over the same period.

Diet

The role of dietary factors is controversial. Observational studies have shown that diets low in antioxidants, such as vitamin C and vitamin A, magnesium, selenium, and omega-3 polyunsaturated fats (fish oil), or high in sodium and omega-6 polyunsaturates are associated with an increased risk of asthma. However, interventional studies have not supported an important role for these dietary factors. Obesity is also an independent risk factor for asthma, particularly in women, but the mechanisms are thus far unknown.



Air Pollution

There is no doubt that air pollutants, such as sulfur dioxide, ozone, and diesel particulates, may trigger asthma symptoms, but the role of different air pollutants in the etiology of the disease is much less certain. Most evidence argues against an important role for air pollution as asthma is no more prevalent in cities with a high ambient level of traffic pollution than in rural areas with low levels of pollution. Asthma had a much lower prevalence in East Germany compared to West Germany despite a much higher level of air pollution, but since reunification these differences have decreased as eastern Germany has become more affluent. Indoor air pollution may be more important with exposure to nitrogen oxides from cooking stoves and exposure to passive cigarette smoke. There is some evidence that maternal smoking is a risk factor for asthma, but it is difficult to dissociate this from an increased risk of respiratory infections.

Exercises

1. Comprehension questions I: Please answer the following questions:

1. Explain respiratory diseases (the three categories)
2. What is dyspnea?
3. What is cough?
4. What is wheezing?
5. Explain the inhalation exposures causing respiratory diseases.
6. What are the symptoms of respiratory diseases?
7. Is simple observation of a patient informative? Why?
8. What is auscultation?
9. What is egophony?
10. What are examinations for respiratory diseases?

2. Fill in the blanks with appropriate words given below:

Hypoxemic associated attention investigation

As stated earlier, rheumatologic disease may manifest primarily as lung disease. Owing to this association, particular _____ should be paid to joint and skin examination. Clubbing can be found in many lung diseases, including cystic fibrosis, IPF, and lung cancer, although it can also be _____ with inflammatory bowel disease or as a congenital finding of no clinical importance. Patients with COPD do not usually have clubbing; thus, this sign should warrant an _____ for second process, most commonly an unrecognized bronchogenic carcinoma, in these patients. Cyanosis is seen in _____ respiratory disorders that result in more than 5 g/dL deoxygenated hemoglobin.

3. Comprehension questions II: Please answer the following questions based on the information in the passage only:

1. What is asthma?
2. How much is the prevalence of asthma?
3. What is atopy?
4. Name the triggers for asthma.
5. What is intrinsic asthma?
6. What are the risk factors for asthma?
7. What is the relation between asthma and genetics?
8. What are the environmental factors?

4. Please analyze the following terms:

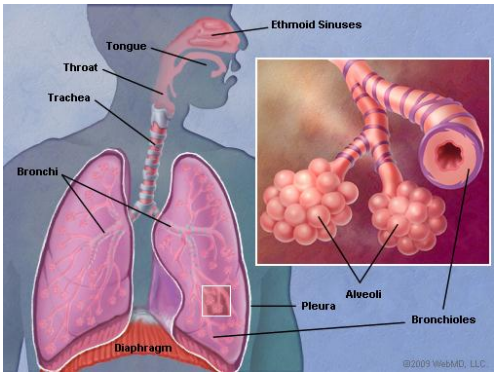
Atopy
Reunification
predisposition
hyperresponsiveness
Endogenous
Mycoplasma
Dermatophagoides
Pteronyssinus

Unit 6: Diseases of the Respiratory System: Pneumonia

Reading 1

Pathophysiology

Pneumonia results from the proliferation of microbial pathogens at the alveolar level and the host's response to those pathogens. Microorganisms gain access to the lower respiratory tract in several ways. The most common is by aspiration from the oropharynx. Small-volume aspiration occurs frequently during sleep (especially in the elderly) and in patients with decreased levels of consciousness. Many pathogens are inhaled as contaminated droplets. Rarely, pneumonia occurs via hematogenous spread (e.g., from tricuspid endocarditis) or by contiguous extension from an infected pleural or mediastinal space.



Mechanical factors are critically important in host defense. The hairs and turbinates of the nares capture larger inhaled particles before they reach the lower respiratory tract. The branching architecture of the tracheobronchial tree traps particles on the airway lining, where mucociliary clearance and local antibacterial factors either clear or kill the potential pathogen. The gag reflex and the cough mechanism offer critical protection from aspiration. In addition, the normal flora adhering to mucosal cells of the oropharynx, whose components are remarkably constant, prevents pathogenic bacteria from binding and thereby decreases the risk of pneumonia caused by these more virulent bacteria.

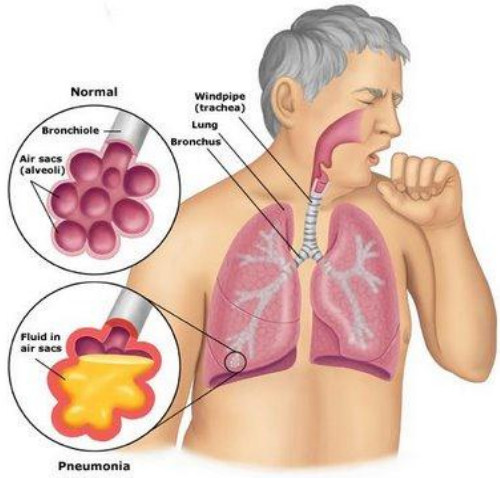
When these barriers are overcome or when the microorganisms are small enough to be inhaled to the alveolar level, resident alveolar macrophages are extremely efficient at clearing and killing pathogens. Macrophages are assisted by local proteins (e.g., surfactant proteins A and D) that have intrinsic opsonizing properties or antibacterial or antiviral activity. Once engulfed by the macrophage, the pathogens—even if they are not killed—are eliminated via either the mucociliary elevator or the lymphatics and no longer represent an infectious challenge. Only when the capacity of the alveolar macrophages to ingest or kill the microorganisms is exceeded does clinical pneumonia become manifest. In that situation, the alveolar macrophages initiate the inflammatory response to bolster lower respiratory tract defenses. The host inflammatory response, rather than the proliferation of microorganisms, triggers the clinical syndrome of pneumonia. The release of inflammatory mediators, such as interleukin (IL)-1 and tumor necrosis factor (TNF), results in fever. Chemokines, such as IL-8 and granulocyte colony-stimulating factor, stimulate the release of neutrophils and their attraction to the lung, producing both peripheral leukocytosis and increased purulent secretions. Inflammatory mediators released by macrophages and the newly recruited neutrophils create an alveolar capillary leak equivalent to that seen in the acute respiratory distress syndrome (ARDS), although in pneumonia this leak is localized (at least initially). Even erythrocytes can cross the alveolar-

capillary membrane, with consequent hemoptysis. The capillary leak results in a radiographic infiltrate and rales detectable on auscultation, and hypoxemia results from alveolar filling. Moreover, some bacterial pathogens appear to interfere with the hypoxemic vasoconstriction that would normally occur with fluid-filled alveoli, and this interference can result in severe hypoxemia. Increased respiratory drive in the systemic inflammatory response syndrome leads to respiratory alkalosis. Decreased compliance due to capillary leak, hypoxemia, increased respiratory drive, increased secretions, and occasionally infection-related bronchospasm all lead to dyspnea. If severe enough, the changes in lung mechanics secondary to reductions in lung volume and compliance and the intrapulmonary shunting of blood may cause the patient's death.

Pathology

Classic pneumonia evolves through a series of pathologic changes. The initial phase is one of *edema*, with the presence of a proteinaceous exudate—and often of bacteria—in the alveoli. This phase is rarely evident in clinical or autopsy specimens because it is so rapidly followed by a *red hepatization* phase. The presence of erythrocytes in the cellular intraalveolar exudate gives this second stage its name, but neutrophil influx is more important from the standpoint of host defense. Bacteria are occasionally seen in pathologic specimens collected during this phase. In the third phase, *gray hepatization*, no new erythrocytes are extravasating, and those already present have been lysed and degraded. The neutrophil is the predominant cell, fibrin deposition is abundant, and bacteria have disappeared. This phase corresponds with successful containment of the infection and improvement in gas exchange. In the final phase, *resolution*, the macrophage reappears as the dominant cell type in the alveolar space, and the debris of neutrophils, bacteria, and fibrin has been cleared, as has the inflammatory response.

This pattern has been described best for lobar pneumococcal pneumonia and may not apply to pneumonias of all etiologies, especially viral or *Pneumocystis* pneumonia. In VAP, respiratory bronchiolitis may precede the development of a radiologically apparent infiltrate. Because of the microaspiration mechanism, a bronchopneumonia pattern is most common in nosocomial pneumonias, whereas a lobar pattern is more common in bacterial CAP. Despite the radiographic appearance, viral and *Pneumocystis* pneumonias represent alveolar rather than interstitial processes.



Reading 2

Epidemiology

In the United States, ~80% of the 4 million CAP cases that occur annually are treated on an outpatient basis, and ~20% are treated in the hospital. CAP results in more than 600,000 hospitalizations, 64 million days of restricted activity, and 45,000 deaths annually. The overall yearly cost associated with CAP is estimated at $9–10 billion. The incidence rates are highest at

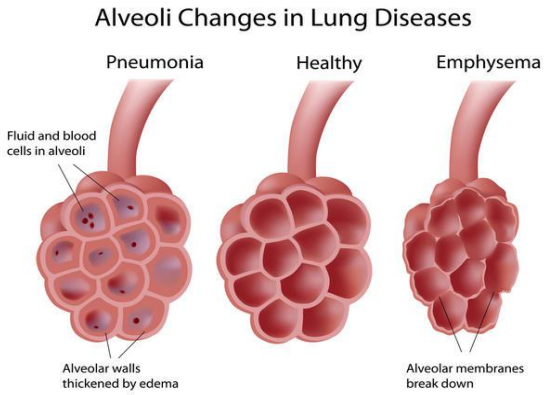
the extremes of age. The overall annual rate in the United States is 12 cases per 1000 persons, but the figure increases to 12–18 per 1000 among children <4 years of age and to 20 per 1000 among persons >60 years of age.

The risk factors for CAP in general and for pneumococcal pneumonia in particular have implications for treatment regimens. Risk factors for CAP include alcoholism, asthma, immunosuppression, institutionalization, and an age of 70 years versus 60–69 years. Risk factors for pneumococcal pneumonia include dementia, seizure disorders, heart failure, cerebrovascular disease, alcoholism, tobacco smoking, chronic obstructive pulmonary disease (COPD), and HIV infection. CA-MRSA pneumonia is more likely in patients with skin colonization or infection with CA-MRSA.

Enterobacteriaceae tend to infect patients who have recently been hospitalized and/or received antibiotic therapy or who have comorbidities such as alcoholism, heart failure, or renal failure. *P. aeruginosa* is a particular problem in patients with severe structural lung disease, such as bronchiectasis, cystic fibrosis, or severe COPD. Risk factors for *Legionella* infection include diabetes, hematologic malignancy, cancer, severe renal disease, HIV infection, smoking, male gender, and a recent hotel stay or ship cruise. (Many of these risk factors would now reclassify as HCAP some cases that were previously designated CAP.)

Clinical Manifestations

CAP can vary from indolent to fulminant in presentation and from mild to fatal in severity. The various signs and symptoms that depend on the progression and severity of the infection include both constitutional findings and manifestations limited to the lung and associated structures. In light of the pathobiology of the disease, many of the findings are to be expected.



The patient is frequently febrile with tachycardia or may have a history of chills and/or sweats. Cough may be either nonproductive or productive of mucoid, purulent, or blood-tinged sputum. Depending on severity, the patient may be able to speak in full sentences or may be very short of breath. If the pleura is involved, the patient may experience pleuritic chest pain. Up to 20% of patients may have gastrointestinal symptoms such as nausea, vomiting, and/or diarrhea. Other symptoms may include fatigue, headache, myalgias, and arthralgias.

Translation

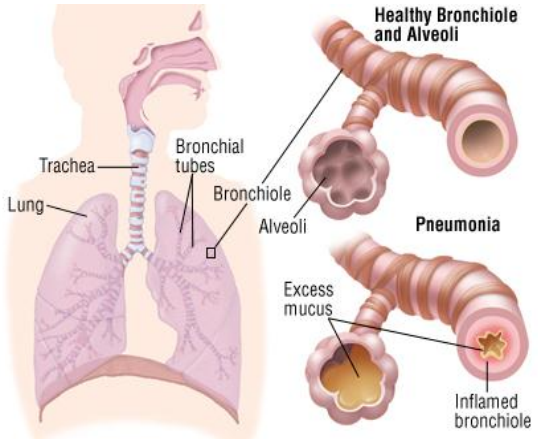
Treatment: Community-Acquired Pneumonia

Site of Care

The cost of inpatient management exceeds that of outpatient treatment by a factor of 20, and hospitalization accounts for most CAP-related expenditures. Thus the decision to admit a patient with CAP to the hospital has considerable implications. Certain patients clearly can be managed at home, and others clearly require treatment in the hospital, but the choice is sometimes difficult. Tools that objectively assess the risk of adverse outcomes, including severe illness and death, can minimize unnecessary hospital admissions. There are currently two sets of criteria: the Pneumonia Severity Index (PSI), a prognostic model used to identify patients at low

risk of dying; and the CURB-65 criteria, a severity-of-illness score.

To determine the PSI, points are given for 20 variables, including age, coexisting illness, and abnormal physical and laboratory findings. On the basis of the resulting score, patients are assigned to one of five classes with the following mortality rates: class 1, 0.1%; class 2, 0.6%; class 3, 2.8%; class 4, 8.2%; and class 5, 29.2%. Clinical trials demonstrate that routine use of the PSI results in lower admission rates for class 1 and class 2 patients. Patients in classes 4 and 5 should be admitted to the hospital, while those in class 3 should ideally be admitted to an observation unit until a further decision can be made.



Failure to Improve

Patients who are slow to respond to therapy should be reevaluated at about day 3 (sooner if their condition is worsening rather than simply not improving), and a number of possible scenarios should be considered. A number of noninfectious conditions can mimic pneumonia, including pulmonary edema, pulmonary embolism, lung carcinoma, radiation and hypersensitivity pneumonitis, and connective tissue disease involving the lungs. If the patient has CAP and treatment is aimed at the correct pathogen, the lack of response may be explained in a number of ways. The pathogen may be resistant to the drug selected, or a sequestered focus (e.g., a lung abscess or empyema) may be blocking access of the antibiotic(s) to the pathogen. The patient may be getting either the wrong drug or the correct drug at the wrong dose or frequency of administration. It is also possible that CAP is the correct diagnosis but that an unsuspected pathogen (e.g., CA-MRSA, *M. tuberculosis*, or a fungus) is the cause. Nosocomial superinfections—both pulmonary and extrapulmonary—are possible explanations for failure to improve or worsening. In all cases of delayed response or deteriorating condition, the patient must be carefully reassessed and appropriate studies initiated. These studies may include such diverse procedures as CT and bronchoscopy.

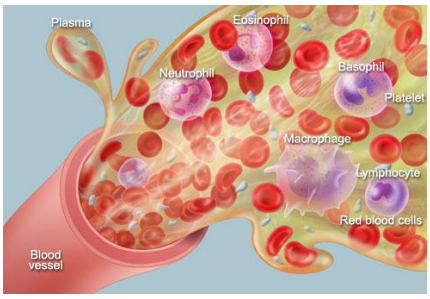
Unit 7: Cardiovascular Disease

Reading 1: Approach to the Patient with Possible Cardiovascular Disease

The Magnitude of the Problem

Cardiovascular diseases comprise the most prevalent serious disorders in industrialized nations and are a rapidly growing problem in developing nations. Age-adjusted death rates for coronary heart disease have declined by two-thirds in the last 4 decades in the United States, reflecting the identification and reduction of risk factors as well as improved treatments and interventions for the management of coronary artery disease, arrhythmias, and heart failure. Nonetheless, cardiovascular diseases remain the most common causes of death, responsible for 35% of all deaths, almost 1 million deaths each year. Approximately one-fourth of these deaths are sudden. In addition, cardiovascular diseases are highly prevalent, diagnosed in 80 million adults, or ~35% of the adult population. The growing prevalence of obesity, type 2 diabetes mellitus, and metabolic syndrome, which are important risk factors for atherosclerosis, now threatens to reverse the progress that has been made in the age-adjusted reduction in the mortality rate of coronary heart disease.

For many years cardiovascular disease was considered to be more common in men than in women. In fact, the percentage of all deaths secondary to cardiovascular disease is higher among women (43%) than among men (37%). In addition, although the absolute number of deaths secondary to cardiovascular disease has declined over the past decades in men, this number has actually risen in women. Inflammation, obesity, type 2 diabetes mellitus, and the metabolic syndrome appear to play more prominent roles in the development of coronary atherosclerosis in women than in men. Coronary artery disease (CAD) is more frequently associated with dysfunction of the coronary microcirculation in women than in men. Exercise electrocardiography has a lower diagnostic accuracy in the prediction of epicardial obstruction in women than in men.



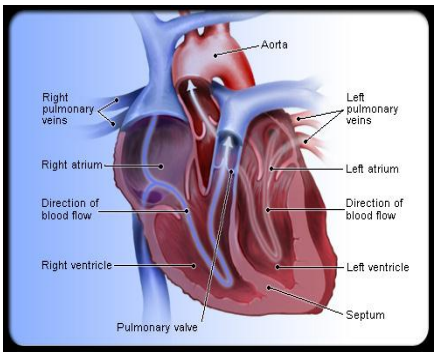
Cardiac Symptoms

The symptoms caused by heart disease result most commonly from myocardial ischemia, disturbance of the contraction and/or relaxation of the myocardium, obstruction to blood flow, or an abnormal cardiac rhythm or rate. Ischemia, which is caused by an imbalance between the heart's oxygen supply and demand, is manifest most frequently as chest discomfort, whereas reduction of the pumping ability of the heart commonly leads to fatigue and elevated intravascular pressure upstream of the failing ventricle. The latter results in abnormal fluid accumulation, with peripheral edema (Chap. 36) or pulmonary congestion and dyspnea. Obstruction to blood flow, as occurs in valvular stenosis, can cause symptoms resembling those of myocardial failure. Cardiac arrhythmias often develop suddenly, and the resulting symptoms and signs—palpitations , dyspnea, hypotension, and syncope (Chap. 20)—generally occur abruptly and may

disappear as rapidly as they develop.

Although dyspnea, chest discomfort, edema, and syncope are cardinal manifestations of cardiac disease, they occur in other conditions as well. Thus, dyspnea is observed in disorders as diverse as pulmonary disease, marked obesity, and anxiety (Chap. 33). Similarly, chest discomfort may result from a variety of noncardiac and cardiac causes other than myocardial ischemia (Chap. 12). Edema, an important finding in untreated or inadequately treated heart failure, also may occur with primary renal disease and in hepatic cirrhosis (Chap. 36). Syncope occurs not only with serious cardiac arrhythmias but in a number of neurologic conditions as well (Chap. 20). Whether heart disease is responsible for these symptoms frequently can be determined by carrying out a careful clinical examination (Chap. 227), supplemented by noninvasive testing using electrocardiography at rest and during exercise, echocardiography, roentgenography, and other forms of myocardial imaging

Myocardial or coronary function that may be adequate at rest may be insufficient during exertion. Thus, dyspnea and/or chest discomfort that appear during activity are characteristic of patients with heart disease, whereas the opposite pattern, i.e., the appearance of these symptoms at rest and their remission during exertion, is rarely observed in such patients. It is important, therefore, to question the patient carefully about the relation of symptoms to exertion.



Many patients with cardiovascular disease may be asymptomatic both at rest and during exertion but may present with an abnormal physical finding such as a heart murmur, elevated arterial pressure, or an abnormality of the electrocardiogram (ECG) or the cardiac silhouette on the chest roentgenogram or other imaging test. It is important to assess the global risk of CAD in asymptomatic individuals, using a combination of clinical assessment and measurement of cholesterol and its fractions, as well as other biomarkers, such as C-reactive protein, in some patients (Chap. 241). Since the first clinical manifestation of CAD may be catastrophic—sudden cardiac death, acute myocardial infarction, or stroke in previous asymptomatic persons—it is mandatory to identify those at high risk of such events and institute further testing and preventive measures.

Diagnosis

As outlined by the New York Heart Association (NYHA), the elements of a complete cardiac diagnosis include the

systematic consideration of the following:

1. *The underlying etiology*. Is the disease congenital, hypertensive, ischemic, or inflammatory in origin?
2. *The anatomical abnormalities*. Which chambers are involved? Are they hypertrophied, dilated, or both? Which valves are affected? Are they regurgitant and/or stenotic? Is there pericardial involvement? Has there been a myocardial infarction?
3. *The physiological disturbances*. Is an arrhythmia present? Is there evidence of congestive heart failure or myocardial ischemia?
4. *Functional disability*. How strenuous is the physical activity required to elicit symptoms? The classification provided by the NYHA has been found to be useful in describing functional disability (Table 226-1).

Table 226–1. New York Heart Association Functional Classification

Class I	Class III
No limitation of physical activity	Marked limitation of physical activity
No symptoms with ordinary exertion	Less than ordinary activity causes symptoms
Class II	Asymptomatic at rest
Slight limitation of physical activity	Class IV
Ordinary activity causes symptoms	Inability to carry out any physical activity without discomfort Symptoms at rest

Source: Modified from The Criteria Committee of the New York Heart Association.

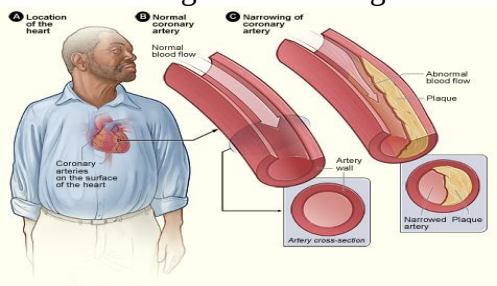
One example may serve to illustrate the importance of establishing a complete diagnosis. In a patient who presents with exertional chest discomfort, the identification of myocardial ischemia as the etiology is of great clinical importance. However, the simple recognition of ischemia is insufficient to formulate a therapeutic strategy or prognosis until the underlying anatomical abnormalities responsible for the myocardial ischemia, e.g., coronary atherosclerosis or aortic stenosis, are identified and a judgment is made about whether other physiologic disturbances that cause an imbalance between myocardial oxygen supply and demand, such as severe anemia, thyrotoxicosis, or supraventricular tachycardia, play contributory roles. Finally, the severity of the disability should govern the extent and tempo of the workup and strongly influence the therapeutic strategy that is selected.

The establishment of a correct and complete cardiac diagnosis usually commences with the history and physical examination (Chap. 227). Indeed, the clinical examination remains the basis for the diagnosis of a wide variety of disorders. The clinical examination may then be supplemented by five types of laboratory tests: (1) ECG (Chap. 228), (2) noninvasive imaging examinations (chest roentgenogram, echocardiogram, radionuclide imaging, computed tomographic imaging, and magnetic resonance imaging (Chap. 229), (3) blood tests to assess risk [e.g., lipid determinations, C-reactive protein (Chap. 241)] or cardiac function [e.g., brain natriuretic peptide (BNP) (Chap. 234)], (4) occasionally specialized invasive examinations [i.e., cardiac catheterization and coronary arteriography (Chap. 230)], and (5) genetic tests to identify monogenic cardiac diseases [e.g., hypertrophic cardiomyopathy (Chap. 238), Marfan syndrome (Chap. 363), and abnormalities of cardiac ion channels that lead to prolongation of the QT interval and an increase in the risk of sudden death (Chap. 233)]. These tests are becoming more widely available.

Reading 2

Family History

In eliciting the history of a patient with known or suspected cardiovascular disease, particular attention should be directed to the family history. Familial clustering is common in many forms of heart disease. Mendelian transmission of single-gene defects may occur, as in hypertrophic cardiomyopathy, Marfan syndrome, and sudden death associated with a prolonged QT syndrome (Chap. 233). Premature coronary disease and essential hypertension, type 2 diabetes mellitus, and hyperlipidemia (the most important risk factors for coronary artery disease) are usually polygenic disorders. Although familial transmission may be less obvious than in the monogenic disorders, it is helpful in assessing risk and prognosis in polygenic disorders. Familial clustering of cardiovascular diseases not only may occur on a genetic basis but also may be related to familial dietary or behavior patterns such as excessive ingestion of salt or calories and cigarette smoking.



Assessment of Functional Impairment

When an attempt is made to determine the severity of functional impairment in a patient with heart disease, it is helpful to ascertain the level of activity and the rate at which it is performed before symptoms develop. Thus, it is not sufficient to state that the patient complains of dyspnea. The breathlessness that occurs after running up two long flights of stairs denotes far less functional impairment than do similar symptoms that occur after taking a few steps on level ground. Also, the degree of customary physical activity at work and during recreation should be considered. The development of two-flight dyspnea in a well-conditioned marathon runner may be far more significant than the development of one-flight dyspnea in a previously sedentary person. The history should include a detailed consideration of the patient's therapeutic regimen. For example, the persistence or development of edema, breathlessness, and other manifestations of heart failure in a patient who is receiving optimal doses of diuretics and other therapies for heart failure is far graver than are similar manifestations in the absence of treatment. Similarly, the presence of angina pectoris despite treatment with optimal doses of multiple antianginal drugs is more serious than it is in a patient on no therapy. In an effort to determine the progression of symptoms, and thus the severity of the underlying illness, it may be useful to ascertain what, if any, specific tasks the patient could have carried out 6 months or 1 year earlier that he or she cannot carry out at present.

Translation

Pitfalls in Cardiovascular Medicine

Increasing subspecialization in internal medicine and the perfection of advanced diagnostic techniques in cardiology can lead to several undesirable consequences. Examples include the following:

1. Failure by the *noncardiologist* to recognize important cardiac manifestations of systemic illnesses. For example, the presence of mitral stenosis, patent foramen ovale, and/or transient atrial arrhythmia should be considered in a patient with stroke, or the presence of pulmonary hypertension and cor pulmonale should be considered in a patient with scleroderma or Raynaud's syndrome. A cardiovascular examination should be carried out to identify and estimate the severity of the cardiovascular involvement that accompanies many noncardiac disorders.

2. Failure by the *cardiologist* to recognize underlying systemic disorders in patients with heart disease. For example, hyperthyroidism should be considered in an elderly patient with atrial fibrillation and unexplained heart failure, and Lyme disease should be considered in a patient with an unexplained fluctuating atrioventricular block. A cardiovascular abnormality may provide the clue critical to the recognition of some systemic disorders. For instance, an unexplained pericardial effusion may provide an early clue to the diagnosis of tuberculosis or a neoplasm.
3. Overreliance on and overutilization of laboratory tests, particularly invasive techniques, for the evaluation of the cardiovascular system. Cardiac catheterization and coronary arteriography (Chap. 230) provide precise diagnostic information that may be crucial in developing a therapeutic plan in patients with known or suspected CAD. Although a great deal of attention has been directed to these examinations, it is important to recognize that they serve to *supplement*, not *supplant*, a careful examination carried out with clinical and noninvasive techniques. A coronary arteriogram should not be performed in lieu of a careful history in patients with chest pain suspected of having ischemic heart disease. Although coronary arteriography may establish whether the coronary arteries are obstructed and to what extent, the results of the procedure by themselves often do not provide a definitive answer to the question of whether a patient's complaint of chest discomfort is attributable to coronary atherosclerosis and whether or not revascularization is indicated.

Despite the value of invasive tests in certain circumstances, they entail some small risk to the patient, involve discomfort and substantial cost, and place a strain on medical facilities. Therefore, they should be carried out only if the results can be expected to modify the patient's management.

Disease Prevention and Management

The prevention of heart disease, especially of CAD, is one of the most important tasks of primary care health givers as well as cardiologists. Prevention begins with risk assessment, followed by attention to lifestyle, such as achieving optimal weight, physical activity, smoking cessation, and then aggressive treatment of all abnormal risk factors, such as hypertension, hyperlipidemia, and diabetes mellitus (Chap. 344).

After a complete diagnosis has been established in patients with known heart disease, a number of management options are usually available. Several examples may be used to demonstrate some of the principles of cardiovascular therapeutics:

1. In the absence of evidence of heart disease, the patient should be clearly informed of this assessment and *not* be asked to return at intervals for repeated examinations. If there is no evidence of disease, such continued attention may lead to the patient's developing inappropriate concern about the possibility of heart disease.
2. If there is no evidence of cardiovascular disease but the patient has one or more risk factors for the development of ischemic heart disease (Chap. 243), a plan for their reduction should be developed and the patient should be retested at intervals to assess compliance and efficacy in risk reduction.

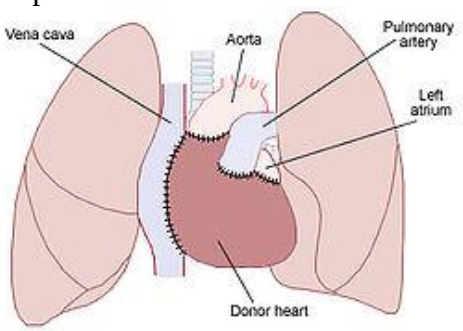
3. Asymptomatic or mildly symptomatic patients with valvular heart disease that is anatomically severe should be evaluated periodically, every 6 to 12 months, by clinical and noninvasive examinations. Early signs of deterioration of ventricular function may signify the need for surgical treatment before the development of disabling symptoms, irreversible myocardial damage, and excessive risk of surgical treatment (Chap. 237).
4. In patients with CAD (Chap. 243), available practice guidelines should be considered in the decision on the form of treatment (medical, percutaneous coronary intervention, or surgical revascularization). Mechanical revascularization may be employed too frequently in the United States and too infrequently in Eastern Europe and developing nations. The mere presence of angina pectoris and/or the demonstration of critical coronary arterial narrowing at angiography should not reflexively evoke a decision to treat the patient by revascularization. Instead, these interventions should be limited to patients with CAD whose angina has not responded adequately to medical treatment or in whom revascularization has been shown to improve the natural history (e.g., acute coronary syndrome or multivessel CAD with left ventricular dysfunction).

Unit 8: Cardiac Transplantation and Prolonged Assisted Circulation

Reading 1

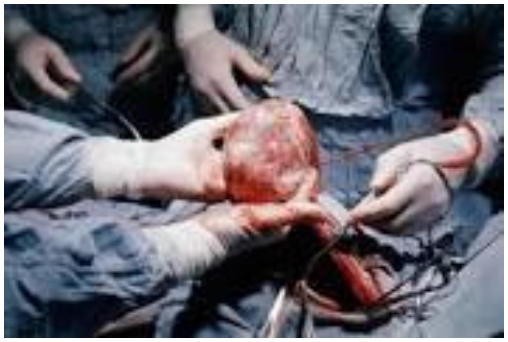
Introduction

Advanced or end-stage heart failure is an increasingly frequent sequela, as progressively more effective palliation for the earlier stages of heart disease and prevention of sudden death associated with heart disease become more widely recognized and employed (Chap. 234). When patients with end-stage or refractory heart failure are identified, the physician is faced with the decision of advising compassionate end-of-life care or choosing to recommend extraordinary life-extending measures. For the occasional patient who is relatively young and without serious comorbidities, the latter may represent a reasonable option. Current therapeutic options are limited to cardiac transplantation (with the option of mechanical cardiac assistance as a "bridge" to transplantation) or (at least in theory) the option of permanent mechanical assistance of the circulation. In the future, it is possible that genetic modulation of ventricular function or cell-based cardiac repair will be options for such patients. Currently, both approaches are considered to be experimental.



Cardiac Transplantation

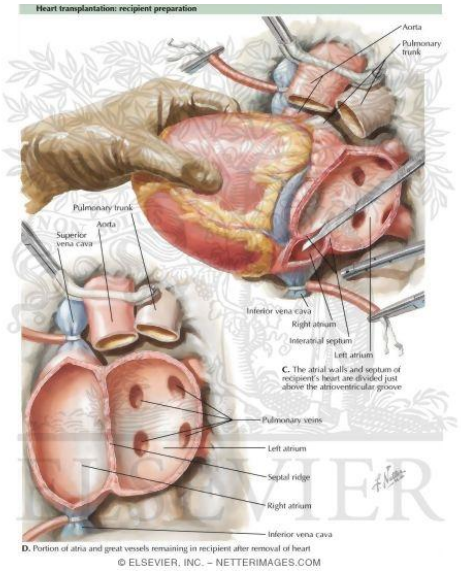
Surgical techniques for orthotopic transplantation of the heart were devised in the 1960s and taken into the clinical arena in 1967. The procedure did not gain widespread clinical acceptance until the introduction of "modern" and more effective immunosuppression in the early 1980s. By the 1990s, the demand for transplantable hearts met, and then exceeded, the available donor supply and leveled off at about 4,000 heart transplants annually worldwide, according to data from the Registry of the International Society for Heart and Lung Transplantation (ISHLT). Subsequently, heart transplant activity in the United States has remained stable at 2,200/year, but worldwide activity reported to this registry has decreased somewhat. This apparent decline in numbers may be a result of the fact that reporting is legally mandated in the United States, but not elsewhere, and several countries have started their own databases.



Surgical Technique

Donor and recipient hearts are excised in virtually identical operations with incisions made across the atria and atrial septum at the midatrial level (leaving the posterior walls of the atria in place) and across the great vessels just above the semilunar valves. The donor heart is generally "harvested" in an anatomically identical manner by a separate surgical team and transported from the donor hospital in a bag of iced saline solution and then is

reanastomosed into the waiting recipient in the orthotopic or normal anatomic position. The only change in surgical technique since this method was first described has been a movement in recent years to move the right atrial anastamosis back to the level of the superior and inferior vena cavae to better preserve right atrial geometry and prevent atrial arrhythmias. Both methods of implantation leave the recipient with a surgically denervated heart that does not respond to any direct sympathetic or parasympathetic stimuli but does respond to circulating catecholamines. The physiologic responses of the denervated heart to the demands of exercise are atypical but quite adequate to carry on normal physical activity.



Donor Allocation System

In the United States the allocation of donor organs is accomplished under the supervision of the United Network for Organ Sharing (UNOS), a private organization under contract to the federal government. The United States is divided geographically into eleven regions for donor heart allocation. Allocation of donor hearts within a region is decided according to a system of priority that takes into account (1) the severity of illness, (2) geographic distance from the donor, and (3) patient time on the waiting list. A physiologic limit of 3 h of "ischemic" (out-of-body) time for hearts precludes a national sharing of hearts. This allocation system design is reissued annually and is responsive to input from a variety of constituencies, including both donor families and transplant professionals.

At the current time, highest priority according to severity of illness is assigned to patients requiring hospitalization at the transplant center for IV inotropic support with a pulmonary artery catheter in place for hemodynamic monitoring or to patients requiring mechanical circulatory support [i.e., intra-aortic balloon pump (IABP), right or left ventricular assist device (RVAD, LVAD), extracorporeal membrane oxygenation (ECMO), or mechanical ventilation]. Second highest priority is given to patients requiring ongoing inotropic support, but without a pulmonary artery catheter in place. All other patients have priority according to their time accrued on the waiting list, and matching is achieved only according to ABO blood group compatibility and gross body size compatibility, although some patients who are "pre-sensitized" and have preexisting anti-HLA antibodies (commonly multiparous women or patients previously multiply transfused) undergo prospective cross-matching with the donor. While HLA matching of donor and recipient would be ideal, the relatively small numbers of patients, as well as the time constraints involved, make such matching impractical.

Reading 2

Indications/Contraindications

Heart failure is an increasingly common cause of death, particularly in the elderly. Most patients, who reach what has recently

been categorized as stage D, or refractory end-stage heart failure, are appropriately treated with compassionate end-of-life care. A subset of such patients who are younger and without significant comorbidities can be considered as candidates for heart transplantation. Exact criteria vary in different centers but generally take into consideration the patient's physiologic age and the existence of comorbidities such as peripheral or cerebrovascular disease, obesity, diabetes, cancer, or chronic infection.

Results

A registry organized by the ISHLT has tracked worldwide and U.S. survival rates after heart transplantation since 1982. The most recent update reveals 83% and 76% survival 1 and 3 years posttransplant, or a posttransplant "half-life" of 10.00 years **(Fig. 235-1)**. The quality of life in these patients is generally excellent, with well over 90% of patients in the registry returning to normal and unrestricted function following transplantation.

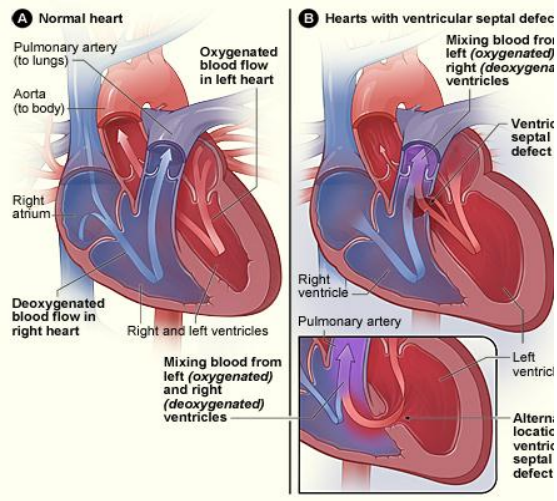
Immunosuppression

Medical regimens employed to provide suppression of the normal immune response to a solid organ allograft vary from center to center and are in a constant state of evolution, as more effective agents with improved side-effect profiles and less toxicity are introduced. All currently used regimens are nonspecific, providing general hyporeactivity to foreign antigens rather than donor-specific hyporeactivity, and also providing the attendant, and unwanted, susceptibility to infections and malignancy. Most cardiac transplant programs currently use a three-drug regimen including a calcineurin inhibitor (cyclosporine or tacrolimus), an inhibitor of T cell proliferation or differentiation (azathioprine, mycophenolate mofetil, or sirolimus), and at least a short initial course of glucocorticoids. Many programs also include an initial "induction" course of polyclonal or monoclonal anti-T cell antibodies in the perioperative period to decrease the frequency or severity of early posttransplant rejection. Most recently introduced have been monoclonal antibodies (daclizumab and basiliximab) that block the interleukin 2 receptor and may provide prevention of allograft rejection without additional global immunosuppression.

Diagnosis of cardiac allograft rejection is usually made with the use of endomyocardial biopsy, either done on a surveillance basis or in response to clinical deterioration. Biopsy surveillance is performed on a regular basis in most programs for the first year postoperatively and for the first five years in many programs. Therapy consists of augmentation of immunosuppression, the intensity and duration of which is dictated by the severity of the rejection.

Translation

Congenital Heart Disease in the Adult:
Introduction
A little over a hundred years ago, Sir William Osler, in his classic textbook *The Principles and Practice of Medicine* (New York, Appleton & Co, 1892, pp 659–663), devoted only five pages to "Congenital Affections of the Heart," with the first sentence declaring, that "[t]hese [disorders] have only limited clinical interest, as in a large proportion of cases the anomaly is not compatible with life, and in others nothing can be done to remedy the defect or even to relieve symptoms." Fortunately, in the intervening century, considerable progress has been made in understanding the basis for these disorders and their effective treatment.



The most common birth defects are cardiovascular in origin. These malformations are due to complex multifactorial genetic and environmental causes, but recognized chromosomal aberrations and mutations of single genes account for <10% of all cardiac malformations. Congenital heart disease (CHD) complicates 1% of all live births in the general population—about 40,000 births/year—but occurs more frequently in the offspring (about 4–5%) of women with CHD. Owing to the remarkable surgical advances over the last 60 years, >90% of afflicted neonates and children now reach adulthood; women with CHD may now frequently successfully bear children after competent repairs. As such, the population with CHD is steadily increasing. Women with aortic disease (e.g., aortic coarctation or Marfan's syndrome) risk aortic dissection. Patients with cyanotic heart disease, pulmonary hypertension, or Marfan's syndrome with a dilated aortic root generally should not become pregnant; those with correctable lesions should be counseled about the risks of pregnancy with an uncorrected malformation versus repair and later pregnancy.

More than one million adults with operated or unoperated CHD live in the United States today and, thus, outnumber the 800,000 children with CHD. Because true surgical cures are rare, and all repairs—be they palliative or corrective—may leave residua, sequelae, or complications, most require some degree of lifetime expert surveillance. The anatomic and physiologic changes in the heart and circulation due to any specific CHD lesion are not static but, rather, progress from prenatal life to adulthood. Malformations that are benign or escape detection in childhood may become clinically significant in the adult. For example, a functionally normal congenitally bicuspid aortic valve may thicken and calcify with time, resulting in significant aortic stenosis; a well-tolerated left-to-right shunt of an atrial septal defect (ASD) may result in cardiac decompensation or pulmonary hypertension only after the fourth to fifth decade.

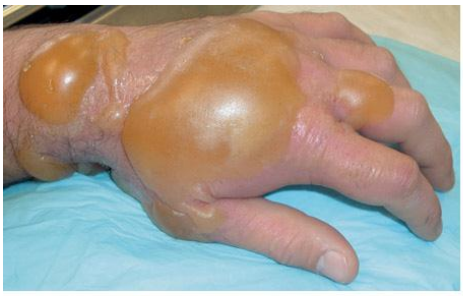
Unit 9: Chemical Terrorism

Reading 1

Introduction

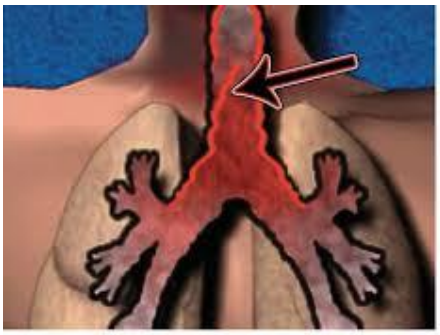
The use of chemical warfare agents (CWAs) in modern warfare dates back to World War I (WWI). Most recently, sulfur mustard and nerve agents were used by Iraq against the Iranian military and Kurdish civilians. Since the Japanese sarin attacks in 1994–1995 and the terrorist strikes of September 11, 2001, the all too real possibility of chemical or biological terrorism against civilian populations anywhere in the world has attracted increased attention.

Military planners consider the WWI blistering agent sulfur mustard and the organophosphorus nerve agents as the most likely agents to be used on the battlefield. In a civilian or terrorist scenario, the choice widens considerably. For example, many of the chemical warfare agents of WWI, including chlorine, phosgene, and cyanide, are used today in large amounts in industry. They are produced in chemical plants, are stockpiled in large tanks, and travel up and down highways and railways in large tanker cars. The rupture of any of these agents by accident or purposely could cause many injuries and deaths. Countless hazardous materials (HAZMATs) that are not used on the battlefield can be used as terrorist weapons. Some of them, including insecticides and ammonia, could wreak as much damage and injury as the weaponized chemical agents.



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

In a recent example, insurgents in Iraq used chlorine gas released from tankers after explosions as a crude form of chemical weaponry. Using this gas, they killed 12 people and intoxicated more than 140 others in three attacks in February 2007. Table 222-1 describes the physical appearance and initial physiologic effects, and Table 222-2 provides guidelines for immediate treatment of chlorine intoxication. Nonetheless, the focus of this chapter is on the blister and nerve chemical warfare agents, which have been employed in battle and against civilians and have demonstrated a significant public health impact.



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Many mistakenly believe that chemical attacks will always be so severe that little can be done except to bury the dead. History proves the opposite. Even in WWI, when IV fluids, endotracheal tubes, and

antibiotics were unavailable, the mortality rate among U.S. forces on the battlefield from chemical warfare agents, chiefly sulfur mustard and the pulmonary intoxicants, was only 1.9%. That was far lower than the 7% mortality rate from conventional wounds. In the 1995 Tokyo subway sarin incident, among the 5500 patients who sought medical attention at hospitals, 80% of whom were not actually symptomatic, only 12 died. Recent events should produce not a fatalistic attitude but a realistic wish to understand the pathophysiology of the syndromes these agents cause, with a view to treating expeditiously all patients who present for care and an expectation of saving the vast majority. As we prepare to defend our civilian population from the effects of chemical terrorism, we also must consider the fact that terrorism itself can produce sequelae such as physiologic or neurologic effects that may resemble the effects of nonlethal exposures to CWAs. These effects are due to a general fear of chemicals, fear of decontamination, fear of protective ensemble, or other phobic reactions.

Many writers have pointed out the increased difficulty in differentiating between stress reactions and nerve agent—induced organic brain syndromes. Knowledge of the behavioral effects of CWAs and their medical countermeasures is imperative to ensure that military and civilian medical and mental health organizations can deal with possible incidents involving weapons of mass destruction

Reading 2

Vesicants

Sulfur Mustard

Sulfur mustard has been a military threat since it first appeared on the battlefield in Belgium during WWI. In modern times it remains a threat on the battlefield as well as a potential terrorist threat for bioterrorism because of simplicity of manufacture and extreme effectiveness. Sulfur mustard accounted for 70% of the 1.3 million chemical casualties in WWI. Occasional cases occur in the United States in people exposed to WWI and WWII-era munitions.

Mechanism

Sulfur mustard constitutes both a vapor and a liquid threat to all exposed epithelial surfaces. The effects are delayed, appearing hours after exposure. The organs most commonly affected are the skin (with erythema and vesicles), eyes (ranging from mild conjunctivitis to severe eye damage), and airways (ranging from mild upper airway irritation to severe bronchiolar damage). After exposure to large quantities of mustard, precursor cells of the bone marrow are damaged, leading to pancytopenia and secondary infection. The gastrointestinal mucosa may be damaged, and there are sometimes central nervous system (CNS) signs of unknown mechanism. No specific antidotes exist; management is entirely supportive. Immediate decontamination of the liquid is the only way to reduce damage. Complete decontamination in 2 minutes stops clinical injury; decontamination at 5 minutes will reduce skin injury by 50%. Table 222-2

lists approaches to decontamination of mustard and other CWAs.

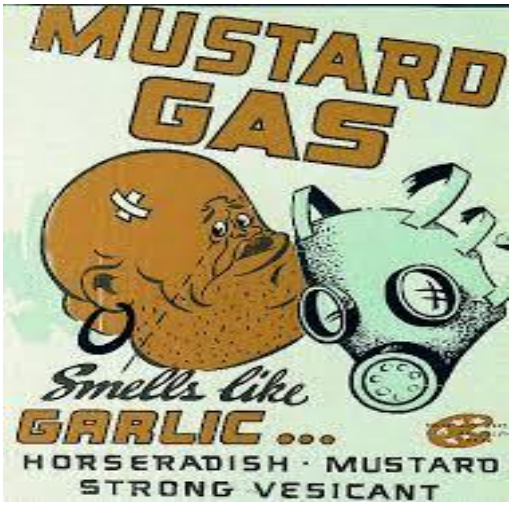
Mustard dissolves slowly in aqueous media such as sweat, but once dissolved, it rapidly forms extremely reactive cyclic ethylene sulfonium ions, which react with cell proteins, cell membranes, and especially DNA in rapidly dividing cells. The ability of mustard to react with and alkylate DNA gives rise to the effects by which it has been characterized as "radiomimetic," similar to radiation injury. Mustard has many biologic actions, but its actual mechanism of action is largely unknown. Much of the biologic damage from mustard results from DNA alkylation and cross-linking in rapidly dividing cells: corneal epithelium, basal keratinocytes, bronchial mucosal epithelium, gastrointestinal mucosal epithelium, and bone marrow precursor cells. This may lead to cellular death and inflammatory reactions. In the skin, proteolytic digestion of anchoring filaments at the epidermal-dermal junction may be the major mechanism of action resulting in blister formation. Mustard also has mild cholinergic activity, which may be responsible for effects such as early gastrointestinal and CNS symptoms.

Mustard reacts with tissue within minutes of entering the body. Its circulating half-life in unaltered form is extremely brief.

Clinical Features

Topical effects of mustard occur in the skin, airways, and eyes, with the eyes being most sensitive, followed by the airways. Absorbed mustard may produce effects in the bone marrow, gastrointestinal tract, and CNS. Direct injury to the gastrointestinal tract also may occur after ingestion of the compound through contamination of water or food.

Erythema is the mildest and earliest form of mustard skin injury. It resembles sunburn and is associated with pruritus, burning, or stinging pain. Erythema begins to appear within 2 hours to 2 days after vapor exposure. Time of onset depends on severity of exposure, ambient temperature and humidity, and type of skin. The most sensitive sites are the warm moist locations and thin delicate skin, such as the perineum, external genitalia, axillae, antecubital fossae, and neck.

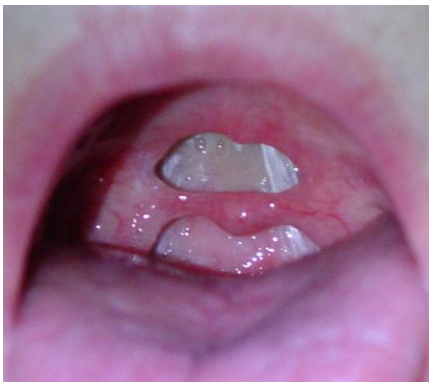


Within the erythematous areas, small vesicles can develop, which may later coalesce to form bullae (Fig. 222-1). The typical bulla is large, dome-shaped, flaccid, thin-walled, translucent, and surrounded by erythema. The blister fluid, a transudate, is clear to straw colored and becomes yellow, tending to coagulate. The fluid does not contain mustard and is not

itself a vesicant. Lesions from high-dose liquid exposure may develop a central zone of coagulation necrosis with blister formation at the periphery. These lesions take longer to heal and are more prone to secondary infection than are the uncomplicated lesions seen at lower exposure levels. Severe lesions may require skin grafting.

The primary airway lesion is necrosis of the mucosa with possible damage to underlying smooth muscle. The damage begins in the upper airways and descends to the lower airways in a dose-dependent manner. Usually the terminal airways and alveoli are affected only as a terminal event. Pulmonary edema is not usually present unless the damage is very severe, and then it becomes hemorrhagic.

The earliest effects from mustard and perhaps the only effects from a low concentration involve the nose, sinuses, and pharynx. There may be irritation or burning of the nares, epistaxis, sinus pain, and pharyngeal pain. As the concentration increases, laryngitis, voice changes, and nonproductive cough develop. Damage to the trachea and upper bronchi leads to a productive cough. Lower airway involvement causes dyspnea, severe cough, and increasing quantities of sputum. Terminally, there may be necrosis of the smaller airways with hemorrhagic edema into surrounding alveoli. Hemorrhagic pulmonary edema is rare.



Necrosis of airway mucosa causes "pseudomembrane" formation. These membranes may cause obstruction of the bronchi. During WWI, high-dose mustard exposure caused acute death via this mechanism in a small minority of cases

The eyes are the organs most sensitive to mustard vapor injury. The latent period is shorter for eye injury than for skin injury and is also exposure concentration—dependent. After low-dose vapor exposure, irritation evidenced by reddening of the eyes may be the only effect. As the dose increases, the injury includes progressively more severe conjunctivitis, photophobia, blepharospasm, pain, and corneal damage

About 90% of eye injuries related to mustard heal in 2 weeks to 2 months without sequelae. Scarring between the iris and the lens may follow severe effects; this scarring may restrict pupillary movements and predispose victims to glaucoma. The most severe damage is caused by liquid mustard. After extensive eye exposure, severe corneal damage with possible perforation of the cornea and loss of the eye can occur. In some individuals, a latent chronic keratitis sometimes associated with corneal ulcerations has been described as early as 8 months and as late as 20 years after initial exposure.

The mucosa of the gastrointestinal tract is susceptible to mustard damage from either systemic absorption or ingestion of the agent. Mustard exposure in small amounts will cause nausea and vomiting lasting up to 24 hours. The mechanism of the nausea and vomiting is not understood, but mustard does have a cholinergic-like effect. The CNS effects of mustard also remain poorly defined. Large exposures can cause seizures in animals. Reports from WWI and from the Iran-Iraq war described people exposed to small amounts of mustard acting sluggish, apathetic, and

lethargic. These reports suggest that minor psychological problems could linger for a year or longer.

The cause of death in the majority of mustard poisoning cases is sepsis and respiratory failure. Mechanical obstruction via pseudomembrane formation and agent-induced laryngospasm is important in the first 24 hours, but only in cases of severe exposure. From the third through the fifth day after exposure, one can expect a secondary pneumonia due to bacterial invasion of denuded necrotic mucosa. The third wave of death is caused by agent-induced bone marrow suppression, which peaks 7–21 days after exposure and causes death via sepsis.

Translation

Treatment: Sulfur Mustard

A patient severely ill from mustard poisoning requires the general supportive care provided for any severely ill patient as well as the specific care given to a burn patient. Liberal use of systemic analgesics, maintenance of fluid and electrolyte balance, nutrition, appropriate antibiotics, and other supportive measures are necessary (Table 222-2).

The management of a patient exposed to mustard may range from simple, as in the provision of symptomatic care for a sunburn-like erythema, to complex, as in providing total management for a severely ill patient with burns, immunosuppression, and multisystem involvement. Before raw denuded areas of skin develop, especially with less severe exposures, topical cortisone creams or lotions may be of benefit. Some very basic research data point to the early use of anti-inflammatory preparations. Small blisters (<1–2 cm) should be left intact. Because larger bullae eventually will break, they should be unroofed carefully. Denuded areas should be irrigated three to four times daily with saline, other sterile solutions, or soapy water and then liberally covered with the topical antibiotic of choice, such as silver sulfadiazine or mafenide acetate, to a thickness of 1–2 mm. Some physicians advocate sterile needle drainage of large blisters, collapsing the blister roof to form a sterile dressing. Mustard blister fluid does not contain sulfur mustard, only sterile tissue fluid. Health care staff should not fear possible contamination. If an antibiotic cream is not available, sterile petrolatum will be useful. Modified Dakins solution (sodium hypochlorite 0.5%) was used both in WWI and in Iranian casualties (1984–1987) for field-expedient irrigation and antisepsis. Large areas of vesication require hospitalization, IV therapy, and whirlpool bath irrigation.

Systemic analgesics should be used liberally, particularly before manipulation of the patient. Monitoring of fluids and electrolytes is important in any sick patient, but it must be recognized that fluid loss is not of the magnitude seen with thermal burns. Overly rigorous hydration seems to have precipitated pulmonary edema in a few Iranian casualties sent to European hospitals.

Conjunctival irritation from a low vapor exposure will respond to any of a number of available ophthalmic solutions after the eyes are irrigated thoroughly. A topical antibiotic applied several times a day will reduce the incidence and severity of infection. Animal laboratory data have shown remarkable results with commercially available topical antibiotic/glucocorticoid ophthalmologic ointments applied early. An ophthalmologist should be consulted. Topical glucocorticoids are not of proven value, but their use during the first few hours or days might significantly reduce inflammation and subsequent damage. Further use should be relegated to an ophthalmologist.

Vaseline or a similar substance should be applied regularly to the edges of the lids to prevent them from sticking together. Topical analgesics may be useful initially if blepharospasm is too severe to permit an adequate examination; however, topical analgesics have limited value.

A productive cough and dyspnea accompanied by fever and leukocytosis occurring within 12–24 hours are indicative of a chemical pneumonitis. The clinician must resist the urge to use prophylactic antibiotics for this process. Infection often occurs on the third to fifth day and is signaled by an increased fever, pulmonary infiltrate, and an increase in sputum production with a change in color. Appropriate antibiotic therapy should await confirmation by Gram stain and, later, positive culture and sensitivity.

Unit 10: Poisoning and Drug Overdosage

Reading 1

Introduction

Poisoning refers to the development of dose-related adverse effects following exposure to chemicals, drugs, or other xenobiotics. To paraphrase Paracelsus, the dose makes the poison. In excessive amounts, substances that are usually innocuous, such as oxygen and water, can cause toxicity. Conversely, in small doses, substances commonly regarded as poisons, such as arsenic and cyanide, can be consumed without ill effect. Although most poisons have predictable dose-related effects, individual variability in the response to a given dose may occur because of genetic polymorphism, enzymatic induction or inhibition in the presence of other xenobiotics, or acquired tolerance. Poisoning may be local (e.g., skin, eyes, or lungs) or systemic depending on the route of exposure, the chemical and physical properties of the poison, and its mechanism of action. The severity and reversibility of poisoning also depend on the functional reserve of the individual or target organ, which is influenced by age and preexisting disease.

Epidemiology

More than 5 million poison exposures occur in the United States each year. Most are acute, accidental (unintentional), involve a single agent, occur in the home, result in minor or no toxicity, and involve children younger than 6 years of age. Pharmaceuticals are involved in 47% of exposures and 84% of serious or fatal poisonings. Unintentional exposures can result from the improper use of chemicals at work or play; label misreading; product mislabeling; mistaken identification of unlabeled chemicals; uninformed self-medication; and dosing errors by nurses, pharmacists, physicians, parents, and the elderly. Excluding the recreational use of ethanol, attempted suicide (deliberate self-harm) is the most common reported reason for intentional poisoning. Recreational use of prescribed and over-the-counter drugs for psychotropic or euphoric effects (abuse) or excessive self-dosing (misuse) are increasingly common and may also result in unintentional self-poisoning.

About 20–25% of exposures require bedside health professional evaluation, and 5% of all exposures require hospitalization. Poisonings account for 5–10% of all ambulance transports, emergency department visits, and intensive care unit admissions. Up to 30% of psychiatric admissions are prompted by attempted suicide via overdosage. Overall, the mortality rate is low: <1% of all exposures. It is much higher (1–2%) in hospitalized patients with intentional (suicidal) overdose, who account for the majority of

serious poisonings. Acetaminophen is the pharmaceutical agent most often implicated in fatal poisoning. Overall, carbon monoxide is the leading cause of death from poisoning, but this is not reflected in hospital or poison center statistics because patients with such poisoning are typically dead when discovered and are referred directly to medical examiners.

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Diagnosis

Although poisoning can mimic other illnesses, the correct diagnosis can usually be established by the history, physical examination, routine and toxicologic laboratory evaluations, and characteristic clinical course. The *history* should include the time, route, duration, and circumstances (location, surrounding events, and intent) of exposure; the name and amount of each drug, chemical, or ingredient involved; the time of onset, nature, and severity of symptoms; the time and type of first-aid measures provided; and the medical and psychiatric history.

In many cases the patient is confused, comatose, unaware of an exposure, or unable or unwilling to admit to one. Suspicious circumstances include unexplained sudden illness in a previously healthy person or a group of healthy people; a history of psychiatric problems (particularly depression); recent changes in health, economic status, or social relationships; and onset of illness while working with chemicals or after ingesting food, drink (especially ethanol), or medications. Patients who become ill soon after arriving from a foreign country or being arrested for criminal activity should be suspected of "body packing" or "body stuffing" (ingesting or concealing illicit drugs in a body cavity). Relevant history may be available from family, friends, paramedics, police, pharmacists, physicians, and employers, who should be questioned regarding the patient's habits, hobbies, behavior changes, available medications, and antecedent events. A search of clothes, belongings, and place of discovery may reveal a suicide note or a container of drugs or chemicals. The imprint code on pills and the label on chemical products may be used to identify the ingredients and potential toxicity of a suspected poison by consulting a reference text, a computerized database, the manufacturer, or a regional poison information center. Occupational exposures require review of any available material safety data sheet (MSDS) from the worksite.

The *physical examination* should focus initially on the vital signs, cardiopulmonary system, and neurologic status. The neurologic examination should include documentation of neuromuscular abnormalities such as dyskinesia, dystonia,

fasciculations, myoclonus, rigidity, and tremors. The patient should also be examined for evidence of trauma and underlying illnesses. Focal neurologic findings are uncommon in poisoning, and their presence should prompt evaluation for a structural central nervous system (CNS) lesion. Examination of the eyes (for nystagmus, pupil size and reactivity), abdomen (for bowel activity and bladder size), and skin (for burns, bullae, color, warmth, moisture, pressure sores, and puncture marks) may reveal findings of diagnostic value. When the history is unclear, all orifices should be examined for the presence of chemical burns and drug packets. The odor of breath or vomitus and the color of nails, skin, or urine may provide important diagnostic clues.

The diagnosis of poisoning in cases of unknown etiology primarily relies on pattern recognition. The first step is to assess the pulse, blood pressure, respiratory rate, temperature, and neurologic status and characterize the overall physiologic state as **stimulated**, **depressed**, **discordant**, or **normal (Table e50–1)**. Obtaining a complete set of vital signs and reassessing them frequently are critical. Measuring core temperature is especially important, even in difficult or combative patients, since temperature elevation is the most reliable prognosticator of poor outcome in poisoning or drug withdrawal. The next step is to consider the underlying causes of the physiologic state and attempt to identify a pathophysiologic pattern or toxic syndrome (*toxidrome*) based on the observed findings. Assessing the severity of physiologic derangements is useful in this regard and also for monitoring the clinical course and response to treatment. The final step is to attempt to identify the particular agent involved by looking for unique or relatively poison-specific physical or ancillary test abnormalities.

Distinguishing among toxidromes based on the physiologic state is summarized below.

Reading 2

Treatment: Poisoning and Drug Overdose

General Principles

Treatment goals include support of vital signs, prevention of further poison absorption (decontamination), enhancement of poison elimination, administration of specific antidotes, and prevention of reexposure (Table e50–3).

Table e50–3 Fundamentals of Poisoning Management

Supportive Care	
Airway protection Oxygenation/ventilation Treatment of arrhythmias Hemodynamic support	Treatment of seizures Correction of temperature abnormalities Correction of metabolic derangements Prevention of secondary complications
Prevention of Further Poison Absorption	
Gastrointestinal decontamination Gastric lavage Activated charcoal Whole-bowel irrigation Dilution Endoscopic/surgical removal	Decontamination of other sites Eye decontamination Skin decontamination Body cavity evacuation
Enhancement of Poison Elimination	
Multiple-dose activated charcoal Alteration of urinary pH Chelation	Extracorporeal removal Hemodialysis Hemoperfusion Hemofiltration Plasmapheresis Exchange transfusion Hyperbaric oxygenation
Administration of Anti-dotes	
Neutralization by antibodies Neutralization by chemical binding	Metabolic antagonism Physiologic antagonism
Prevention of Reexposure	

Supportive Care	
Adult education Child-proofing	Notification of regulatory agencies Psychiatric referral

Specific treatment depends on the identity of the poison, the route and amount of exposure, the time of presentation relative to the time of exposure, and the severity of poisoning. Knowledge of the offending agents' pharmacokinetics and pharmacodynamics is essential.

During the *pretoxic phase*, prior to the onset of poisoning, decontamination is the highest priority, and treatment is based solely on the history. The maximum potential toxicity based on the greatest possible exposure should be assumed. Since decontamination is more effective when accomplished soon after exposure, and when the patient is asymptomatic, the initial history and physical examination should be focused and brief. It is also advisable to establish IV access and initiate cardiac monitoring, particularly in patients with potentially serious ingestions or unclear histories.

When an accurate history is not obtainable and a poison causing delayed toxicity ("toxic time-bomb") or irreversible damage is suspected, blood and urine should be sent for appropriate toxicologic screening and quantitative analysis. During absorption and distribution, blood levels may be greater than those in tissue and may not correlate with toxicity. However, high blood levels of agents whose metabolites are more toxic than the parent compound (acetaminophen, ethylene glycol, or methanol) may indicate the need for additional interventions (antidotes, dialysis). Most patients who remain or become asymptomatic 6 h after ingestion are unlikely to develop subsequent toxicity and can be discharged safely. Longer observation will be necessary for patients who have ingested toxic time-bombs, agents that are slowly absorbed, slowly distributed to their sites of action, require metabolic activation, or disrupt metabolic processes (Table e50–1). During the *toxic phase*, the time between the onset of poisoning and the peak effects, management is based primarily on clinical and laboratory findings. *Effects after an overdose usually begin sooner, peak later, and last longer than they do after a therapeutic dose*. A drug's published pharmacokinetic profile in standard references such as the *Physician's Desk Reference* (*PDR*) is usually different from its toxicokinetic profile in overdose. Resuscitation and stabilization are the first priority. Symptomatic patients should have an IV line, oxygen saturation determination, cardiac monitoring, and continuous observation. Baseline laboratory, ECG, and x-ray evaluation may also be appropriate. Intravenous glucose (unless the serum level is documented to be normal), naloxone, and thiamine should be considered in patients with altered mental status, particularly those with coma or seizures. Decontamination should also be considered, but it is less likely to be effective during this phase than during the pretoxic one. Measures that enhance poison elimination may shorten the duration and severity of the toxic phase. However, they are not without risk, which must be weighed against the potential benefit. Diagnostic certainty (usually via laboratory confirmation) is generally a prerequisite. Intestinal (or "gut") dialysis with repetitive doses of activated charcoal (also termed *multidose activated charcoal*) can enhance the elimination of selected poisons such as theophylline or

carbamazepine. Urinary alkalinization may enhance the elimination of salicylates and a small number of other poisons. Chelation therapy can enhance the elimination of selected metals. Extracorporeal elimination methods are effective for many poisons, but their expense and risk make their use reasonable only in patients who would otherwise have an unfavorable outcome.

During the *resolution phase* of poisoning, supportive care and monitoring should continue until clinical, laboratory, and ECG abnormalities have resolved. Since chemicals are eliminated sooner from the blood than from tissues, blood levels are usually lower than tissue levels during this phase and again may not correlate with toxicity. This is particularly true when extracorporeal elimination procedures are used. Redistribution from tissues may cause a rebound increase in the blood level after termination of these procedures. When a metabolite is responsible for toxic effects, continued treatment might be necessary in the absence of clinical toxicity or abnormal laboratory studies.

Translation

Respiratory Care

Endotracheal intubation for protection against the aspiration of gastrointestinal contents is of paramount importance in patients with CNS depression or seizures as this complication can increase morbidity and mortality rates. Mechanical ventilation may be necessary for patients with respiratory depression or hypoxemia and to facilitate therapeutic sedation or paralysis in order to prevent or treat hyperthermia, acidosis, and rhabdomyolysis associated with neuromuscular hyperactivity. Since clinical assessment of respiratory function can be inaccurate, the need for oxygenation and ventilation is best determined by continuous pulse oximetry or arterial blood-gas analysis. The gag reflex is not a reliable indicator of the need for intubation. A patient with CNS depression may maintain airway patency while being stimulated but not if left alone. Drug-induced pulmonary edema is usually noncardiac rather than cardiac in origin, although profound CNS depression and cardiac conduction abnormalities suggest the latter. Measurement of pulmonary artery pressure may be necessary to establish the cause and direct appropriate therapy. Extracorporeal measures (membrane oxygenation, venoarterial perfusion, cardiopulmonary bypass) and partial liquid (perfluorocarbon) ventilation may be appropriate for severe but reversible respiratory failure.

Cardiovascular Therapy

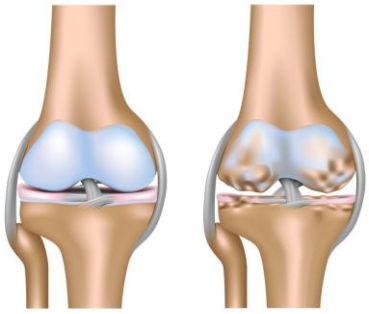
Maintenance of normal tissue perfusion is critical for complete recovery to occur once the offending agent has been eliminated. If hypotension is unresponsive to volume expansion, treatment with norepinephrine, epinephrine, or high-dose dopamine may be necessary. Intraaortic balloon pump counterpulsation and venoarterial or cardiopulmonary perfusion techniques should be considered for severe but reversible cardiac failure. Bradyarrhythmias associated with hypotension generally should be treated as described in Chap. 232. Glucagon, calcium, and high-dose insulin with dextrose may be effective in beta blocker and calcium channel blocker poisoning. Antibody therapy may be indicated for cardiac glycoside poisoning.

Unit 11: Osteoarthritis

Reading 1

Introduction

Osteoarthritis (OA) is the most common type of arthritis. Its high prevalence, especially in the elderly, and the high rate of disability related to disease make it a leading cause of disability in the elderly. Because of the aging of Western populations and because obesity, a major risk factor, is increasing in prevalence, the occurrence of osteoarthritis is on the rise. In the United States, osteoarthritis prevalence will increase by 66–100% by 2020.

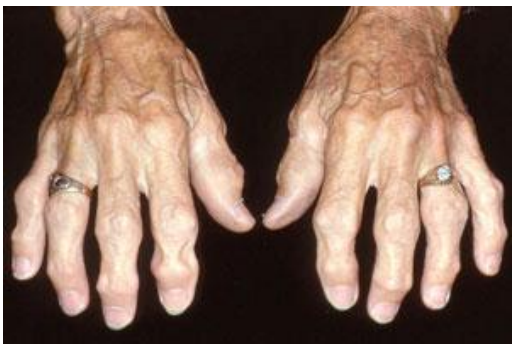


Healthy knee joint Osteoarthritis

OA affects certain joints, yet spares others. Commonly affected joints include the cervical and lumbosacral spine, hip, knee, and first metatarsal phalangeal joint (MTP). In the hands, the distal and proximal interphalangeal joints and the base of the thumb are often affected. Usually spared are the wrist, elbow, and ankle. Our joints were designed, in an evolutionary sense, for brachiating apes, animals that still walked on four limbs. We thus develop OA in joints that were ill designed for human tasks such as pincer grip (OA in the thumb base) and walking upright (OA in knees and hips) Some joints, like the ankles, may be spared because their articular cartilage may be uniquely resistant to loading stresses.

Systemic Risk Factors

Age is the most potent risk factor for OA. Radiographic evidence of OA is rare in individuals under age 40; however, in some joints, such as the hands, OA occurs in >50% of persons over age 70. Aging increases joint vulnerability through several mechanisms. Whereas dynamic loading of joints stimulates cartilage matrix synthesis by chondrocytes in young cartilage, aged cartilage is less responsive to these stimuli. Indeed, because of the poor responsiveness of older cartilage to such stimulation, cartilage transplant operations are far more challenging in older than in younger persons. Partly because of this failure to synthesize matrix with loading, cartilage thins with age, and thinner cartilage experiences higher shear stress at basal layers and is at greater risk of cartilage damage. Also, joint protectors fail more often with age. Muscles that bridge the joint become weaker with age and also respond less quickly to oncoming impulses. Sensory nerve input slows with age, retarding the feedback loop of mechanoreceptors to muscles and tendons related to their tension and position. Ligaments stretch with age, making them less able to absorb impulses. These factors work in concert to increase the vulnerability of older joints to OA.



Older women are at high risk of OA in all joints, a risk that emerges as women reach their sixth decade. While hormone loss with menopause may contribute to this risk, there is little understanding of the unique vulnerability of older women vs. men to OA.

Heritability and Genetics

OA is a highly heritable disease, but its heritability varies by joint. Fifty percent of the hand and hip OA in the community is attributable to inheritance, i.e., to disease present in other members of the family. However, the heritable proportion of knee OA is at most 30%, with some studies suggesting no heritability at all. Whereas many people with OA have disease in multiple joints, this "generalized OA" phenotype is rarely inherited and is more often a consequence of aging.

Emerging evidence has identified genetic mutations that confer a high risk of OA, one of which is a polymorphism within the growth differentiation factor 5 gene. *This polymorphism diminishes the quantity of GDF5, which normally has anabolic effects on the synthesis of cartilage matrix*.

Global Considerations

Hip OA is rare in China and in immigrants from China to the United States. However, OA in the knees is at least as common, if not more so, in Chinese than in whites from the United States, and knee OA represents a major cause of disability in China, especially in rural areas. Anatomic differences between Chinese and white hips may account for much of the difference in hip OA prevalence, with white hips having a higher prevalence of anatomic predispositions to the development of OA. Persons from Africa, but not African Americans, may also have a very low rate of hip OA.

Risk Factors in the Joint Environment

Some risk factors increase vulnerability of the joint through local effects on the joint environment. With changes in joint anatomy, for example, load across the joint is no longer distributed evenly across the joint surface, but rather shows an increase in focal stress. In the hip, three uncommon developmental abnormalities occurring in utero or childhood, congenital dysplasia, Legg-Perthes disease, and slipped capital femoral epiphysis, leave a child with distortions of hip joint anatomy that often lead to OA later in life. Girls are predominantly affected by acetabular dysplasia, a mild form of congenital dislocation, whereas the other abnormalities more often affect boys. Depending on the severity of the anatomic abnormalities, hip OA occurs either in young adulthood (severe abnormalities) or middle age (mild abnormalities).

Major injuries to a joint also can produce anatomic abnormalities that leave the joint susceptible to OA. For example, a fracture through the joint surface often causes OA in joints in which the disease is otherwise rare such as the ankle and the wrist. Avascular necrosis can lead to collapse of dead bone at the articular surface, producing anatomic irregularities and subsequent OA.

Tears of ligamentous and fibrocartilaginous structures that protect the joints, such as the anterior cruciate ligament and the meniscus in the knee and the labrum in the hip, increase joint susceptibility and can lead to premature OA. Meniscal tears increase with age and when chronic are often asymptomatic but lead to adjacent cartilage damage and accelerated osteoarthritis. Even injuries that do not produce diagnosed joint injuries may increase risk of OA, perhaps because the structural injury was not detected at the time. For example, in the Framingham study subjects, men with a history of major knee injury, but no surgery, had a 3.5-fold increased risk for subsequent knee OA.

Another source of anatomic abnormality is malalignment across the joint **(Fig. 332-5)**. This factor has been best studied in the knee, which is the fulcrum of the longest lever arm in the body. Varus (bowlegged) knees with OA are at exceedingly high risk of cartilage loss in the medial or inner compartment of the

knee, whereas valgus (knock-kneed) malalignment predisposes to rapid cartilage loss in the lateral compartment. Malalignment causes this effect by decreasing contact area during loading, increasing stress on a focal area of cartilage, which then breaks down. There is evidence that malalignment in the knee not only causes cartilage loss but leads to underlying bone damage, producing bone marrow lesions seen on MRI. Malalignment in the knee often produces such a substantial increase in focal stress within the knee (as evidenced by its destructive effects on subchondral bone) that severely malaligned knees may be destined to progress regardless of the status of other risk factors

Reading 2

Osteoarthritis

Osteoarthritis is a joint disease that most often affects middle-age to elderly people. It is commonly referred to as OA or as "wear and tear" of the joints, but we now know that OA is a disease of the entire joint, involving the cartilage, joint lining, ligaments, and bone. Although it is more common in older people, it is not really accurate to say that the joints are just "wearing out."

About 27 million Americans are living with OA, the most common form of joint disease. The lifetime risk of developing OA of the knee is about 46%, and the lifetime risk of developing OA of the hip is 25%, according to the Johnston County Osteoarthritis Project, a long-term study from the University of North Carolina and sponsored by the Centers for Disease Control and Prevention (often called the CDC) and the National Institutes of Health.

OA is a top cause of disability in older people. The goal of treatment in OA is to reduce pain and improve function. There is no cure for the disease, but some treatments attempt to slow disease progression.

Fast Facts

- OA is the most common form of joint disease, and is a leading cause of disability in elderly people.
- This arthritis tends to occur in the hand joints, spine, hips, knees, and great toes.
- It is characterized by breakdown of the cartilage (the tissue that cushions the ends of the bones between joints), bony changes of the joints, deterioration of tendons and ligaments, and various degrees of inflammation of the synovium (joint lining).
- Though some of the joint changes are irreversible, most patients will not need joint replacement surgery.
- OA symptoms (what you feel) can vary greatly among patients.
- A rheumatologist can detect arthritis and prescribe the proper treatment.
-

In osteoarthritis, the cartilage between the bones in the joint breaks down (left image). Slowly, affected bones get bigger, as in the hand at right.

What Is Osteoarthritis?

OA is a frequently slowly progressive joint disease typically seen in middle-aged to elderly people.

The disease occurs when the joint cartilage breaks down often because of mechanical stress or biochemical alterations, causing the bone underneath to fail. OA can occur together with other types of arthritis, such as gout or rheumatoid arthritis.
OA tends to affect commonly used joints such as the hands and spine, and the weight-bearing joints such as the hips and knees.

Symptoms include:

- Joint pain and stiffness
- Knobby swelling at the joint
- Cracking or grinding noise with joint movement
- Decreased function of the joint

Who Gets Osteoarthritis?

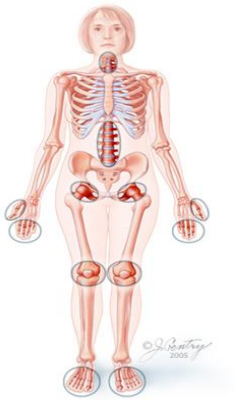
OA affects people of all races and both sexes. Most often, it occurs in patients age 40 and above. However, it can occur sooner if you have other risk factors (things that raise the risk of getting OA).

Risk factors include:

- Older age
- Having family members with OA
- Obesity
- Joint injury or repetitive use (overuse) of joints
- Joint deformity such as unequal leg length, bowlegs or knocked knees

How Is Osteoarthritis Diagnosed?

Most often doctors detect OA based on the typical symptoms (described earlier) and on results of the physical exam. In some cases, X-rays or other imaging tests may be useful to tell the extent of disease or to help rule out other joint problems.



Circles indicate joints that osteoarthritis most often affects.

How Is Osteoarthritis Treated?

There is no proven treatment yet that can reverse joint damage from OA. The goal of treatment is to reduce pain and improve function of the affected joints. Most often, this is possible with a mixture of physical measures and drug therapy and, sometimes, surgery.

Translation

Physical Measures

Weight loss and exercise are useful in OA. Excess weight puts stress on your knee joints and hips and low back. For every 10 pounds of weight you lose over 10 years, you can reduce the chance of developing knee OA by up to 50%. Exercise can improve your muscle strength, decrease joint pain and stiffness, and lower the chance of disability due to OA.

Also helpful are support ("assistive") devices, such as braces or a walking cane, that help you do daily activities. Heat or cold therapy can help relieve OA symptoms for a short time.

Certain alternative treatments such as spa (hot tub), massage, acupuncture and chiropractic manipulation can help relieve pain for a short time. They can be costly, though, and require repeated treatments. Also, the long-term benefits of these alternative (sometimes called complementary or integrative) medicine treatments are unproven but are under study.

Drug Therapy

Forms of drug therapy include topical, oral (by mouth) and injections (shots). You apply topical drugs directly on the skin over the affected joints. These medicines include capsaicin cream, lidocaine and diclofenac gel. Oral pain relievers such as acetaminophen are common first treatments. So are nonsteroidal anti-inflammatory drugs (often called NSAIDs), which decrease swelling and pain.

In 2010, the government (FDA) approved the use of duloxetine (Cymbalta) for chronic (long-term) musculoskeletal pain including from OA. This oral drug is not new. It also is in use for other health concerns, such as mood disorders, nerve pain and fibromyalgia.

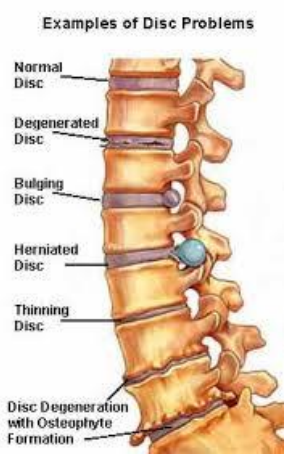
Patients with more serious pain may need stronger medications, such as prescription narcotics.

Joint injections with corticosteroids (sometimes called

cortisone shots) or with a form of lubricant called hyaluronic acid can give months of pain relief from OA. This lubricant is given in the knee, and these shots may help delay the need for a knee replacement by a few years in some patients.

Surgery

Surgical treatment becomes an option for severe cases. This includes when the joint has serious damage, or when medical treatment fails to relieve pain and you have major loss of function. Surgery may involve arthroscopy, repair of the joint done through small incisions (cuts). If the joint damage cannot be repaired, you may need a joint replacement.



Supplements

Many over-the-counter nutrition supplements have been used for treatment of OA. Most lack good research data to support their effectiveness and safety. Among the most widely used are glucosamine/chondroitin sulfate, calcium and vitamin D, and omega-3 fatty acids. To ensure safety and avoid drug interactions, consult your doctor or pharmacist before using any of these supplements. This is especially true when you are combining these supplements with prescribed drugs.

Living with Osteoarthritis

There is no cure for OA, but you can manage how it affects your lifestyle. Some tips include:

- Properly position and support your neck and back while sitting or sleeping.
- Adjust furniture, such as raising a chair or toilet seat.
- Avoid repeated motions of the joint, especially frequent bending.
- Lose weight if you are overweight or obese, which can reduce pain and slow progression of OA.
- Exercise each day.
- Use arthritis support devices that will help you do daily activities.

You might want to work with a physical therapist or occupational therapist to learn the best exercises and to choose arthritis assistive devices.

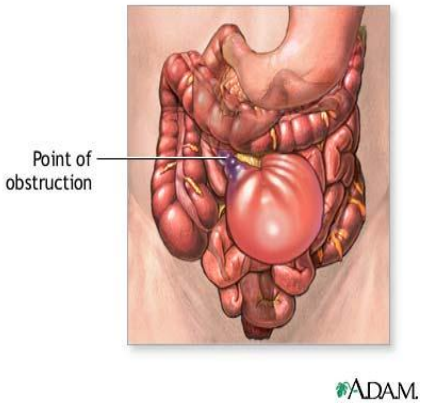
Points to Remember

- OA is the most common form of arthritis and can occur together with other types of arthritis.
- The goal of treatment in OA is to reduce pain and improve function.
- Exercise is an important part of OA treatment because it can decrease joint pain and improve function.
- At present, there is no treatment that can reverse the damage of OA in the joints. Researchers are trying to find ways to slow or reverse this joint damage.

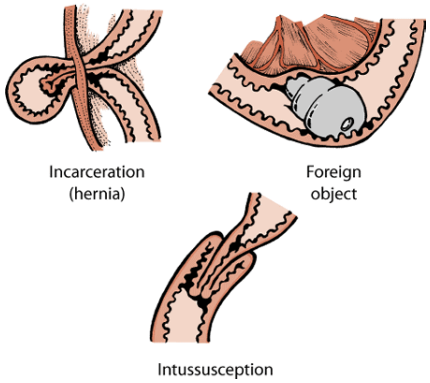
Unit 12: Intestinal Obstruction

Reading 1

Intestinal obstruction and reobstruction are common problems in patients with advanced cancer, particularly colorectal or ovarian carcinoma. However, other cancers, such as lung or breast cancer and melanoma, can metastasize within the abdomen, leading to intestinal obstruction. Typically, obstruction occurs at multiple sites in peritoneal carcinomatosis. Melanoma has a predilection to involve the small bowel; this involvement may be isolated and resection may result in prolonged survival. Intestinal pseudoobstruction is caused by infiltration of the mesentery or bowel muscle by tumor, involvement of the celiac plexus, or paraneoplastic neuropathy in patients with small cell lung cancer. Paraneoplastic neuropathy is associated with IgG antibodies reactive to neurons of the myenteric and submucosal plexuses of the jejunum and stomach. Ovarian cancer can lead to authentic luminal obstruction or to pseudoobstruction that results when circumferential invasion of a bowel segment arrests the forward progression of peristaltic contractions.



The onset of obstruction is usually insidious. Pain is the most common symptom and is usually colicky in nature. Pain can also be due to abdominal distention, tumor masses, or hepatomegaly. Vomiting can be intermittent or continuous. Patients with complete obstruction usually have constipation. Physical examination may reveal abdominal distention with tympany, ascites, visible peristalsis, high-pitched bowel sounds, and tumor masses. Erect plain abdominal films may reveal multiple air-fluid levels and dilation of the small or large bowel. Acute cecal dilation to >12–14 cm is considered a surgical emergency because of the high likelihood of rupture. CT scan is useful in differentiating benign from malignant causes of obstruction in patients who have undergone surgery for malignancy. Malignant obstruction is suggested by a mass at the site of obstruction or prior surgery, adenopathy, or an abrupt transition zone and irregular bowel thickening at the obstruction site. Benign obstruction is more likely when CT shows mesenteric vascular changes, a large volume of ascites, or a smooth transition zone and smooth bowel thickening at the obstruction site. The prognosis for the patient with cancer who develops intestinal obstruction is poor; median survival is 3–4 months. About 25–30% of patients are found to have intestinal obstruction due to causes other than cancer. Adhesions from previous operations are a common benign cause. Ileus induced by vinca alkaloids, narcotics, or other drugs is another reversible cause.



Treatment: Intestinal Obstruction

The management of intestinal obstruction in patients with advanced malignancy depends

on the extent of the underlying malignancy and the functional status of the major organs. The initial management should include surgical evaluation. Operation is not always successful and may lead to further complications with a substantial mortality rate (10–20%). Laparoscopy can diagnose and treat malignant bowel obstruction in some cases. Self-expanding metal stents placed in the gastric outlet, duodenum, proximal jejunum, colon, or rectum may palliate obstructive symptoms at those sites without major surgery. Patients known to have advanced intraabdominal malignancy should receive a prolonged course of conservative management, including nasogastric decompression. Percutaneous endoscopic or surgical gastrostomy tube placement is an option for palliation of nausea and vomiting, the so-called "venting gastrostomy." Treatment with antiemetics, antispasmodics, and analgesics may allow patients to remain outside the hospital. Octreotide may relieve obstructive symptoms through its inhibitory effect on gastrointestinal secretion.

Reading 2

Urinary Obstruction

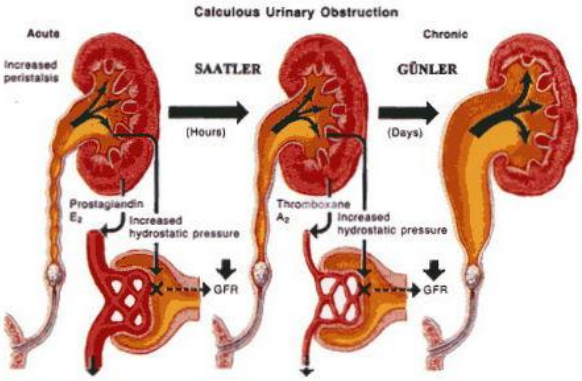
Urinary obstruction may occur in patients with prostatic or gynecologic malignancies, particularly cervical carcinoma; metastatic disease from other primary sites such as carcinomas of the breast, stomach, lung, colon, and pancreas; or lymphomas. Radiation therapy to pelvic tumors may cause fibrosis and subsequent ureteral obstruction. Bladder outlet obstruction is usually due to prostate and cervical cancers and may lead to bilateral hydronephrosis and renal failure.

Flank pain is the most common symptom. Persistent urinary tract infection, persistent proteinuria, or hematuria in patients with cancer should raise suspicion of ureteral obstruction. Total anuria and/or anuria alternating with polyuria may occur. A slow, continuous rise in the serum creatinine level necessitates immediate evaluation. Renal ultrasound is the safest and cheapest way to identify hydronephrosis. The function of an obstructed kidney can be evaluated by a nuclear scan. CT scan can reveal the point of obstruction and identify a retroperitoneal mass or adenopathy.

Translation

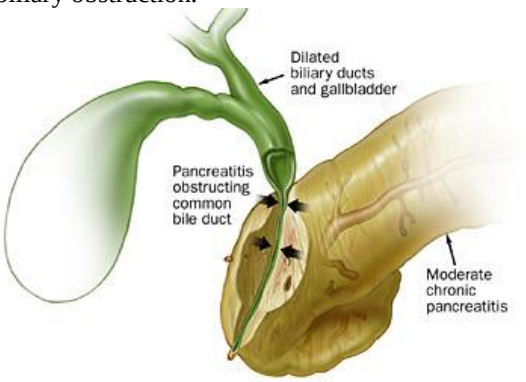
Treatment: Urinary Obstruction

Obstruction associated with flank pain, sepsis, or fistula formation is an indication for immediate palliative urinary diversion. Internal ureteral stents can be placed under local anesthesia. Percutaneous nephrostomy offers an alternative approach for drainage. In the case of bladder outlet obstruction due to malignancy, a suprapubic cystostomy can be used for urinary drainage.



Malignant Biliary Obstruction

This common clinical problem can be caused by a primary carcinoma arising in the pancreas, ampulla of Vater, bile duct, or liver or by metastatic disease to the periductal lymph nodes or liver parenchyma. The most common metastatic tumors causing biliary obstruction are gastric, colon, breast, and lung cancers. Jaundice, light-colored stools, dark urine, pruritus, and weight loss due to malabsorption are usual symptoms. Pain and secondary infection are uncommon in malignant biliary obstruction. Ultrasound, CT scan, or percutaneous transhepatic or endoscopic retrograde cholangiography will identify the site and nature of the biliary obstruction.



Treatment: Malignant Biliary Obstruction

Palliative intervention is indicated only in patients with disabling pruritus resistant to medical treatment, severe malabsorption, or infection. Stenting under radiographic control, surgical bypass, or radiation therapy with or without chemotherapy may alleviate the obstruction. The choice of therapy should be based on the site of obstruction (proximal vs distal), the type of tumor (sensitive to radiotherapy, chemotherapy, or neither), and the general condition of the patient. In the absence of pruritus, biliary obstruction may be a largely asymptomatic cause of death.

Unit 13: Mental Disorders

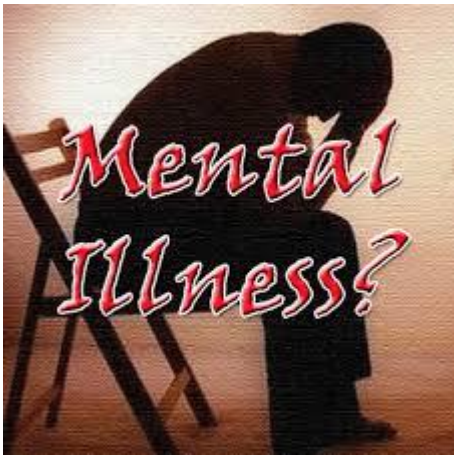
Reading 1

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. The physician should discuss with the patient the reasons for requesting the referral or consultation and provide reassurance that he or she will continue to provide medical care and work collaboratively with the mental health professional. Consultation with a

psychiatrist or transfer of care is appropriate when physicians encounter evidence of psychotic symptoms, mania, severe depression, or anxiety; symptoms of posttraumatic stress disorder (PTSD); suicidal or homicidal preoccupation; or a failure to respond to first-order treatment.

Anxiety Disorders

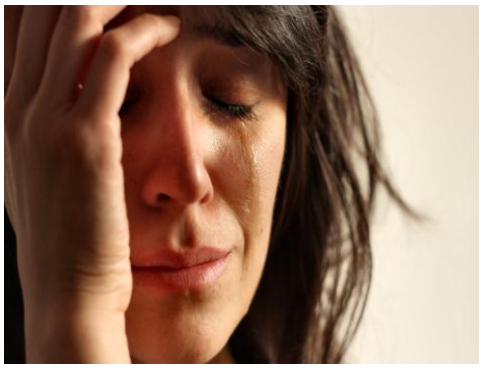
Anxiety disorders, the most prevalent psychiatric illnesses in the general community, are present in 15–20% of medical clinic patients. Anxiety, defined as a subjective sense of unease, dread, or foreboding, can indicate a primary psychiatric condition or can be a component of, or reaction to, a primary medical disease. The primary anxiety disorders are classified according to their duration and course and the existence and nature of precipitants.

When evaluating the anxious patient, the clinician must first determine whether the anxiety antedates or postdates a medical illness or is due to a medication side effect. Approximately one-third of patients presenting with anxiety have a medical etiology for their psychiatric symptoms, but an anxiety disorder can also present with somatic symptoms in the absence of a diagnosable medical condition.

Panic Disorder

Clinical Manifestations

Panic disorder is defined by the presence of recurrent and unpredictable panic attacks, which are distinct episodes of intense fear and discomfort associated with a variety of physical symptoms, including palpitations, sweating, trembling, shortness of breath, chest pain, dizziness, and a fear of impending doom or death (Table 391-1).



Attack

A discrete period of intense fear or discomfort, in which four or more of the following symptoms developed abruptly and reached a peak within 10 minutes:

1. Palpitations, pounding heart, or accelerated heart rate
2. Sweating
3. Trembling or shaking
4. Sensations of shortness of breath or smothering
5. Feeling of choking
6. Chest pain or discomfort
7. Nausea or abdominal distress
8. Feeling dizzy, unsteady, lightheaded, or faint
9. Derealization (feelings of unreality) or depersonalization (being detached from oneself)
10. Fear of losing control or going crazy
11. Fear of dying
12. Paresthesias (numbness or tingling sensations)
13. Chills or hot flushes

Paresthesias, gastrointestinal distress, and feelings of unreality are also common. Diagnostic criteria require at least 1 month of concern or worry about the attacks or a change in behavior related to them. The lifetime prevalence of panic disorder is 1–3%. Panic attacks have a sudden onset, developing within 10 minutes and usually resolving over the course of an hour, and they occur in an unexpected fashion. The frequency and severity of panic attacks vary, ranging from once a week to clusters of attacks separated by months of well-being. The first attack is usually outside the home, and onset is typically in late adolescence to early adulthood. In some individuals, anticipatory anxiety develops over time and results in a generalized fear and a progressive avoidance of places or situations in which a panic attack might recur. Agoraphobia, which occurs commonly in patients with panic disorder, is an acquired irrational fear of being in places where one might feel trapped or unable to escape (Table 391-2). Typically, it leads the patient into a progressive restriction in lifestyle and, in a literal sense, in geography. Frequently, patients are embarrassed that they are housebound and dependent on the company of others to go out into the world and do not volunteer this information; thus physicians will fail to recognize the syndrome if direct questioning is not pursued.

Agoraphobia

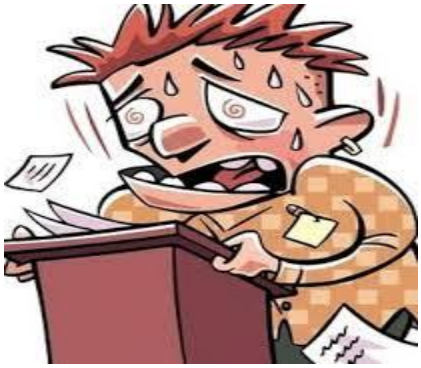
1. Anxiety about being in places or situations from which escape might be difficult (or embarrassing) or in which help may not be available in the event of having an unexpected or situationally predisposed panic attack or panic-like symptoms. Agoraphobic fears typically involve characteristic clusters of situations that include being outside the home alone; being in a crowd or standing in a line; being on a bridge; and traveling in a bus, train, or automobile.
2. The situations are avoided (e.g., travel is restricted) or else are endured with marked distress or with anxiety about having a panic attack or panic-like symptoms, or require the presence of a companion.
3. The anxiety or phobic avoidance is not better accounted for by another mental disorder such as social phobia (e.g., avoidance limited to social situations because of fear of embarrassment), specific phobia (e.g., avoidance limited to a single situation like elevators), obsessive-compulsive disorder (e.g., avoidance of dirt in someone with an obsession about contamination), posttraumatic stress disorder (e.g., avoidance of stimuli associated with a severe stressor), or separation anxiety disorder (e.g., avoidance of leaving home or relatives).

Reading 2

Differential Diagnosis

A diagnosis of panic disorder is made after a medical etiology for the panic attacks has been ruled out. A variety of cardiovascular, respiratory, endocrine, and neurologic conditions can present with anxiety as the chief complaint. Patients with true panic disorder will often focus on one specific feature to the exclusion of others. For example, 20% of patients who present with syncope as a primary medical complaint have a primary diagnosis of a mood, anxiety, or substance-abuse disorder, the most common being panic disorder. The differential diagnosis of panic disorder is complicated by a high rate of comorbidity with other psychiatric conditions, especially alcohol and benzodiazepine abuse, which patients initially use in an attempt at self-medication. Some 75% of panic disorder patients will also

satisfy criteria for major depression at some point in their illness.



When the history is nonspecific, physical examination and focused laboratory testing must be used to rule out anxiety states resulting from medical disorders such as pheochromocytoma, thyrotoxicosis, or hypoglycemia. Electrocardiogram (ECG) and echocardiogram may detect some cardiovascular conditions associated with panic such as paroxysmal atrial tachycardia and mitral valve prolapse. In two studies, panic disorder was the primary diagnosis in 43% of patients with chest pain who had normal coronary angiograms and was present in 9% of all outpatients referred for cardiac evaluation. Panic disorder has also been diagnosed in many patients referred for pulmonary function testing or with symptoms of irritable bowel syndrome.

Translation

Etiology and Pathophysiology

The etiology of panic disorder is unknown but appears to involve a genetic predisposition, altered autonomic responsivity, and social learning. Panic disorder shows familial aggregation; the disorder is concordant in 30–45% of monozygotic twins, and genomewide screens have identified suggestive risk loci. Acute panic attacks appear to be associated with increased noradrenergic discharges in the locus coeruleus. Intravenous infusion of sodium lactate evokes an attack in two-thirds of panic disorder patients, as do the 2-adrenergic antagonist yohimbine, cholecystokinin tetrapeptide (CCK-4), and carbon dioxide inhalation. It is hypothesized that each of these stimuli activates a pathway involving noradrenergic neurons in the locus coeruleus and serotonergic neurons in the dorsal raphe. Agents that block serotonin reuptake can prevent attacks. Panic-disorder patients have a heightened sensitivity to somatic symptoms, which triggers increasing arousal, setting off the panic attack; accordingly, therapeutic intervention involves altering the patient's cognitive interpretation of anxiety-producing experiences as well as preventing the attack itself.

Treatment: Panic Disorder

Achievable goals of treatment are to decrease the frequency of panic attacks and to reduce their intensity. The cornerstone of drug therapy is antidepressant medication (Tables 391-3through391-5). Selective serotonin reuptake inhibitors (SSRIs) benefit the majority of panic disorder patients and do not have the adverse effects of tricyclic antidepressants (TCAs). Fluoxetine, paroxetine, sertraline, and the selective serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine have received approval from the U.S. Food and Drug Administration (FDA) for this indication. These drugs should be started at one-third to one-half of their usual antidepressant dose (e.g., 5–10 mg fluoxetine, 25–50 mg sertraline, 10 mg paroxetine, venlafaxine 37.5 mg). Monoamine oxidase inhibitors (MAOIs) are also effective and may specifically benefit patients who have comorbid features of atypical depression (i.e., hypersomnia and weight gain). Insomnia, orthostatic hypotension, and the need to maintain a low-tyramine diet (avoidance of cheese and wine) have limited their use, however. Antidepressants typically take 2–6 weeks to become effective, and doses may need to be adjusted based upon the clinical response.

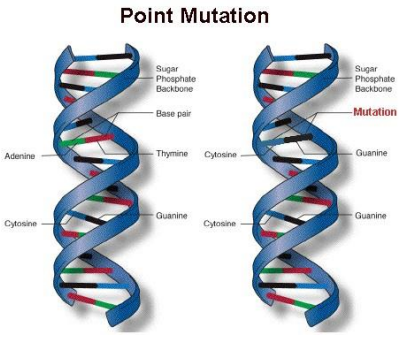
Unit 14: Impact of Genetics on Medical Practice

Reading 1

The beginning of the new millennium was marked by the announcement that the vast majority of the human genome had been sequenced. This milestone in the exploration of the human genome was preceded by numerous conceptual and technologic advances. They include, among others, the elucidation of the DNA double-helix structure, the discovery of restriction enzymes and the polymerase chain reaction (PCR), the development and automatization of DNA sequencing, and the generation of genetic and physical maps by the Human Genome Project (HGP). The consequences of this wealth of knowledge for the practice of medicine are profound. First, the most significant impact of genetics has been to enhance our understanding of disease etiology and pathogenesis. However, genetics is playing an increasingly prominent role in the diagnosis, prevention, and treatment of disease (Chap. 63).

Genetic approaches have proven invaluable for the detection of infectious pathogens and are used clinically to identify agents that are difficult to culture such as mycobacteria, viruses, and parasites. In many cases, molecular genetics has improved the feasibility and accuracy of diagnostic testing and is beginning to open new avenues for therapy, including gene and cellular therapy (Chaps. 68 and 67). Molecular genetics has significantly changed the treatment of human disease. Peptide hormones, growth factors, cytokines, and vaccines can now be produced in large amounts using recombinant DNA technology. Targeted modifications of these peptides provide the practitioner with improved therapeutic tools, as illustrated by genetically modified insulin analogues with more favorable kinetics. There is hope that a better understanding of the genetic basis of human disease will also have an increasing impact on disease prevention.

Genetics has traditionally been viewed through the window of relatively rare single-gene diseases. Taken together, these disorders account for 10% of pediatric admissions and childhood mortality. It is, however, increasingly apparent that virtually every medical condition has a genetic component. As is often evident from a patient's family history, many common disorders such as hypertension, heart disease, asthma, diabetes mellitus, and mental illnesses are significantly influenced by the genetic background. These polygenic or multifactorial (complex) disorders involve the contributions of many different genes, as well as environmental factors that can modify disease risk (Chap. 63). Genome-wide association studies (GWAS) have elucidated numerous disease-associated loci and are providing novel insights into the allelic architecture of complex traits. These studies have been facilitated by the availability of comprehensive catalogues of human single-nucleotide polymorphism (SNP) haplotypes generated through the HapMap Project.



Cancer has a genetic basis since it results from acquired somatic mutations in genes controlling growth, apoptosis, and cellular differentiation. In addition, the development of many cancers is associated with a hereditary predisposition. The prevalence of genetic diseases, combined with their severity and chronic nature, imposes great financial, social, and emotional burdens on society.

Genetics has historically focused predominantly on chromosomal and metabolic disorders, reflecting the long-standing availability of techniques to diagnose these conditions. For example, conditions such as trisomy 21 (Down syndrome) or monosomy X (Turner's syndrome) can be diagnosed using cytogenetics. Likewise, many metabolic disorders (e.g., phenylketonuria, familial hyper–cholesterolemia) are diagnosed using biochemical analyses. Recent advances in DNA diagnostics have extended the field of genetics to include virtually all medical specialties. In cardiology, for example, the molecular basis of inherited cardiomyopathies and ion channel defects that predispose to arrhythmias is being defined. In neurology, genetics has unmasked the pathophysiology of a startling number of neurodegenerative disorders. Hematology has evolved dramatically, from its incipient genetic descriptions of hemoglobinopathies to the current understanding of the molecular basis of red cell membrane defects, clotting disorders, and thrombotic disorders.

New concepts derived from genetic studies can sometimes clarify the pathogenesis of disorders that were previously opaque. For example, although many different genetic defects can cause peripheral neuropathies, disruption of the normal folding of the myelin sheaths is frequently a common final pathway. Several genetic causes of obesity appear to converge on a physiologic pathway that involves products of the proopiomelanocortin polypeptide and the MC4R receptor, thus identifying a key mechanism for appetite control (Chap. 77). A similar phenomenon is emerging for genetically distinct forms of Alzheimer's disease, several of which lead to the formation of neurofibrillary tangles (Chap. 371). The identification of defective genes often leads to the detection of cellular pathways involved in key physiologic processes. Examples include identification of the cystic fibrosis conductance regulator (*CFTR*) gene; the Duchenne's muscular dystrophy (*DMD*) gene, which encodes dystrophin; and the fibroblast growth factor receptor-3 (*FGFR3*) gene, which is responsible for achondroplastic dwarfism. Similarly, transgenic (over)expression, and targeted gene "knock-out" and "knock-in" models help to unravel the physiologic function of genes.

The astounding rate at which new genetic information is being generated creates a major challenge for physicians, health care providers, and basic investigators. The terminology and techniques used for discovery evolve continuously. Much genetic information resides in databases or is being published in basic science journals. Databases provide easy access to the expanding information about the human genome, genetic disease, and genetic testing. For example, several thousand monogenic disorders are summarized in a large, continuously evolving compendium, referred to as the *Online Mendelian Inheritance in Man* (OMIM) catalogue. The ongoing refinement of

bioinformatics is simplifying the access to this daunting onslaught of new information.

Reading 2

Chromosomes and DNA Replication

Size of the Human Genome

The human genome is divided into 23 different chromosomes, including 22 autosomes (numbered 1–22) and the X and Y sex chromosomes. Adult cells are *diploid*, meaning they contain two homologous sets of 22 autosomes and a pair of sex chromosomes. Females have two X chromosomes (XX), whereas males have one X and one Y chromosome (XY). As a consequence of meiosis, germ cells (sperm or oocytes) are haploid and contain one set of 22 autosomes and one of the sex chromosomes. At the time of fertilization, the diploid genome is reconstituted by pairing of the homologous chromosomes from the mother and father. With each cell division (mitosis), chromosomes are replicated, paired, segregated, and divided into two daughter cells.

Although the exact number of genes encoded by the human genome is still unknown, current estimates predict about 23,000 to 25,000 protein-coding genes, a number that is substantially smaller than initially predicted. A *gene* is a functional unit that is regulated by transcription (see below) and encodes an RNA product, which is most commonly, but not always, translated into a protein that exerts activity within or outside the cell. Historically, genes were identified because they conferred specific traits that are transmitted from one generation to the next. Increasingly, they are characterized based on expression in various tissues (transcriptome). The number of genes greatly underestimates the complexity of genetic expression, as single genes can generate multiple spliced messenger RNA (mRNA) products, which are translated into proteins that are subject to complex posttranslational modification such as phosphorylation. *Proteomics*, the study of the proteome using technologies of large-scale protein separation and identification, is focused on protein variation and function. Similarly, the field of *metabolomics* aims at determining the composition and modifications of the *metabolome*, the complement of low-molecular-weight molecules, many of which participate in various metabolic functions. The human *microbiome* refers to the constellation of viruses, bacteria, and fungi that colonize various human tissues. Comprehensive characterization of the microbiome has been made feasible by the availability of high-throughput DNA-sequencing methods. Analyses of genomics, proteomics, metabolomics, and the microbiome are heavily dependent on bioinformatics, and they are beginning to reveal how physiologic or pathologic alterations affect *modular networks* rather than *linear pathways*.

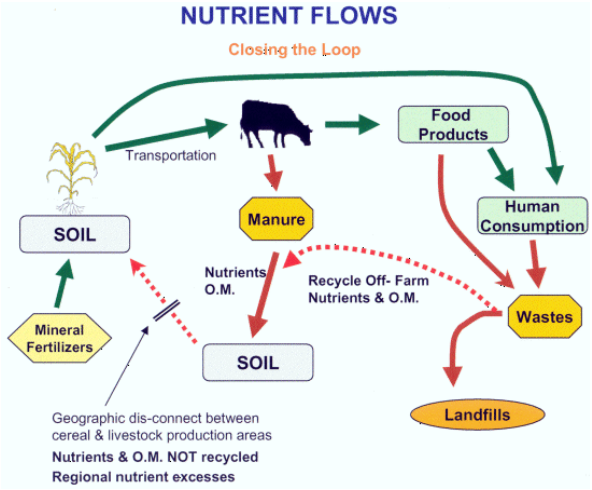
Human DNA consists of 3 billion base pairs (bp) of DNA per haploid genome. DNA length is normally measured in units of 1000 bp (kilobases, kb) or 1,000,000 bp (megabases, Mb). Not all DNA encodes genes. In fact, genes account for only 10–15% of DNA. Much of the remaining DNA consists of highly repetitive sequences, the function of which is poorly understood. These repetitive DNA regions, along with nonrepetitive sequences that do not encode genes, may serve a structural role in the packaging of DNA into chromatin, i.e., DNA bound to histone proteins, and chromosomes. If only 10% of DNA is expressed and there are 25,000 genes, the average gene would be 12 kb in length. Although many genes are about this size, the range is quite broad. For example, some genes are only a few hundred bp, whereas others such as the *DMD* gene, are extraordinarily large (2 Mb).

Unit 15: Nutrient Requirements and Dietary Assessment

Reading 1

Introduction

Nutrients are substances that are not synthesized in sufficient amounts in the body and therefore must be supplied by the diet. Nutrient requirements for groups of healthy persons have been determined experimentally. For good health, we require energy-providing nutrients (protein, fat, and carbohydrate), vitamins, minerals, and water. Human requirements for organic nutrients include 9 essential amino acids, several fatty acids, glucose, 4 fat-soluble vitamins, 10 water-soluble vitamins, dietary fiber, and choline. Several inorganic substances, including 4 minerals, 7 trace minerals, 3 electrolytes, and the ultra trace elements, must also be supplied by diet.



The required amounts of the essential nutrients differ by age and physiologic state. Conditionally essential nutrients are not required in the diet but must be supplied to individuals who do not synthesize them in adequate amounts, such as those with genetic defects, those having pathologic states with nutritional implications, and developmentally immature infants. Many other organic and inorganic compounds present in foods have health effects. For example, lead and pesticide residues may have toxic effects. Essential Nutrient Requirements

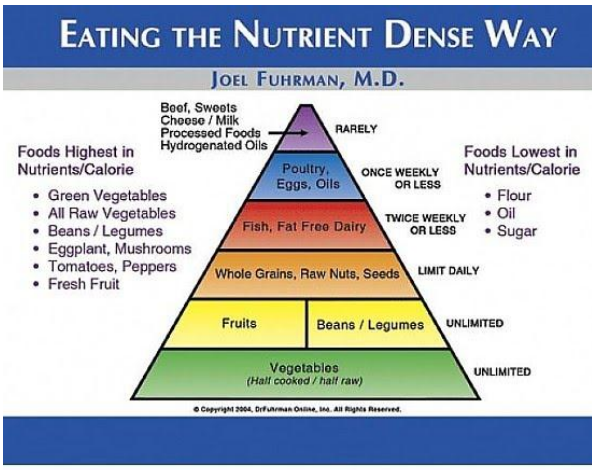
Energy

For weight to remain stable, energy intake must match energy output. The major components of energy output are resting energy expenditure (REE) and physical activity; minor sources include the energy cost of metabolizing food (thermic effect of food or specific dynamic action) and shivering thermogenesis (e.g., cold-induced thermogenesis). The average energy intake is about 2600 kcal/d for American men and about 1900 kcal/d for American women, though these estimates vary with body size and activity level. Formulas for estimating REE are useful for assessing the energy needs of an individual whose weight is stable. Thus, for males, REE = 900 + 10*m*, and for females, REE = 700 + 7*m*, where *m* is mass in kilograms. The calculated REE is then adjusted for physical activity level by multiplying by 1.2 for sedentary, 1.4 for moderately active, or 1.8 for very active individuals. The final figure provides an estimate of total caloric needs in a state of energy balance. For further discussion of energy balance in health and disease.

Protein

Dietary protein consists of both essential and nonessential amino acids that are required for

protein synthesis. The nine essential amino acids are histidine, isoleucine, leucine, lysine, methionine/cystine, phenylalanine/tyrosine, threonine, tryptophan, and valine. Certain amino acids, such as alanine, can also be used for energy and gluconeogenesis. When energy intake is inadequate, protein intake must be increased, because ingested amino acids are diverted into pathways of glucose synthesis and oxidation. In extreme energy deprivation, protein-calorie malnutrition may ensue (Chap. 75).



For adults, the recommended dietary allowance (RDA) for protein is about 0.6 g/kg desirable body mass per day, assuming that energy needs are met and that the protein is of relatively high biologic value. Current recommendations for a healthy diet call for at least 10 to 14% of calories from protein. Most American diets provide at least those amounts. Biologic value tends to be highest for animal proteins, followed by proteins from legumes (beans), cereals (rice, wheat, corn), and roots. Combinations of plant proteins that complement one another in biologic value, or combinations of animal and plant proteins, can increase biologic value and lower total protein requirements.

Protein needs increase during growth, pregnancy, lactation, and rehabilitation after injury or malnutrition. Tolerance to dietary protein is decreased in renal insufficiency (causing uremia) and in liver failure. Normal protein intake can precipitate encephalopathy in patients with cirrhosis of the liver.

Fat and Carbohydrate

Fats are a concentrated source of energy and constitute, on average, 34% of calories in U.S. diets. However, for optimal health, fat intake should total no more than 30% of calories. Saturated fat and trans-fat should be limited to <10% of calories, and polyunsaturated fats to <10% of calories, with monounsaturated fats comprising the remainder of fat intake. At least 45–55% of total calories should be derived from carbohydrates. The brain requires about 100 g/d of glucose for fuel; other tissues use about 50 g/d. Some tissues (e.g., brain and red blood cells) rely on glucose supplied either exogenously or from muscle proteolysis. Over time, adaptations in carbohydrate needs are possible during hypocaloric states.

Reading 2

Water

For adults, 1 to 1.5 mL water per kcal of energy expenditure is sufficient under usual conditions to allow for normal variations in physical activity, sweating, and solute load of the diet. Water losses include 50 to 100 mL/d in the feces; 500 to 1000 mL/d by evaporation or exhalation; and, depending on the renal solute load, 1000 mL/d in the urine. If external losses increase, intakes must increase accordingly to avoid underhydration. Fever increases water losses by approximately 200 mL/d per °C; diarrheal losses vary, but may be as great as 5 L/d in severe diarrhea. Heavy sweating and vomiting also increase water losses. When renal function is normal and solute intakes are adequate, the kidneys can adjust to increased water intake by excreting up to 18 L/d of excess water. However, obligatory urine outputs can compromise hydration status when there is inadequate intake or when losses increase in disease or

kidney damage.

Infants have high requirements for water because of their large ratio of surface area to volume, the limited capacity of the immature kidney to handle high renal solute loads, and their inability to communicate their thirst. Increased water needs during pregnancy are about 30 mL/d. During lactation, milk production increases water requirements so that approximately 1000 mL/d of additional water is needed, or 1 mL for each mL of milk produced. Special attention must be paid to the water needs of the elderly, who have reduced total body water and blunted thirst sensation, and are more likely to be taking medications such as diuretics.

Other Nutrients

Dietary Reference Intakes and Recommended Dietary Allowances

Fortunately, human life and well-being can be maintained within a fairly wide range for most nutrients. However, the capacity for adaptation is not infinite—too much, as well as too little, intake of a nutrient could have adverse effects or alter the health benefits conferred by another nutrient. Therefore, benchmark recommendations regarding nutrient intakes have been developed to guide clinical practice. These quantitative estimates of nutrient intakes are collectively referred to as the *dietary reference intakes* (DRIs). The DRIs supplant the *recommended daily allowances* (RDAs), the single reference values used in the United States until the early 1990s. DRIs include the *estimated average requirement* (EAR) for nutrients as well as other reference values used for dietary planning for individuals: the RDA, the *adequate intake* (AI), and the tolerable *upper level* (UL). The DRI also include acceptable macronutrient distribution ranges (AMDR) for protein, fat, and carbohydrate. The current DRIs for vitamins and elements are provided in Tables 73-1 and 73-2, respectively.

Estimated Average Requirement

When florid manifestations of the classic dietary deficiency diseases such as rickets (deficiency of vitamin D and calcium), scurvy (deficiency of vitamin C), xerophthalmia (deficiency of vitamin A), and protein-calorie malnutrition were common, nutrient adequacy was inferred from the absence of their clinical signs. Later, biochemical and other changes were found to be evident long before the clinical deficiency became apparent. Consequently, criteria of adequacy are now based on biologic markers when they are available. Current efforts focus on the amount of a nutrient that reduces the risk of chronic degenerative diseases. Priority is given to sensitive biochemical, physiologic, or behavioral tests that reflect early changes in regulatory processes; maintenance of body stores of nutrients; or, if available, the amount of a nutrient that minimizes risk of chronic degenerative disease.

The EAR is the amount of a nutrient estimated to be adequate for half of the healthy individuals of a specific age and sex. The types of evidence and criteria used to establish nutrient requirements vary by nutrient, age, and physiologic group. The EAR is not an effective estimate of nutrient adequacy in individuals because it is a median requirement for a group; 50% of individuals in a group fall below the requirement and 50% fall above it. Thus, a person with a usual intake at the EAR has a 50% risk of an inadequate intake. For these reasons, other standards, described below, are more useful for clinical purposes.

Translation

Recommended Dietary Allowances

The RDA is the average daily dietary intake level that meets the nutrient requirements of nearly all healthy persons of a specific sex, age, life stage, or physiologic condition (such as pregnancy or lactation). The RDA is

the nutrient-intake goal for planning diets of individuals.

The RDA is defined statistically as two standard deviations (SD) above the EAR to ensure that the needs of any given individual are met. Recommendations for individuals of a given age, sex, and weight are easily obtained from a Web-based calculator at *http://fnic.nal.usda.gov/interactiveDRI/*. This online tool allows health professionals to calculate daily nutrient recommendations for dietary planning based on the DRIs for individuals.

The RDAs are used to formulate food guides such as the U.S. Department of Agriculture (USDA) Food Guide Pyramid for individuals, to create food-exchange lists for therapeutic diet planning, and as a standard for describing the nutritional content of processed foods and nutrient-containing dietary supplements. The nutrient content in a food is stated by weight or as a percent of the daily value (DV), a variant of the RDA used in food labeling on the nutrition facts panel that, for an adult, represents the highest RDA for an adult consuming 2000 kcal/d.

The risk of dietary inadequacy increases as intake falls below the RDA. However, the RDA is an overly generous criterion for evaluating nutrient adequacy. For example, by definition the RDA exceeds the actual requirements of all but about 2 to 3% of the population. Therefore, many people whose intake falls below the RDA may still be getting enough of the nutrient.

Adequate Intake

It is not possible to set an RDA for some nutrients that do not have an established EAR. In this circumstance, the AI is based on observed, or experimentally determined, approximations of nutrient intakes in healthy people. In the DRIs, AIs rather than RDAs are proposed for infants up to age 1 year, as well as for calcium, chromium, vitamin D, fluoride, manganese, pantothenic acid, biotin, and choline for persons of all ages. Vitamin D and calcium are currently being reevaluated, and more precise values may be available in the near future.

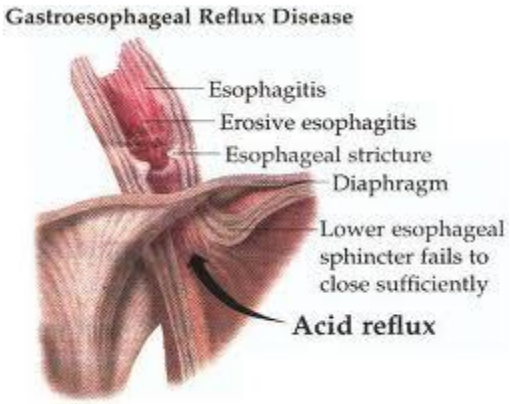
Tolerable Upper Levels of Nutrient Intake

Excessive nutrient intake can disturb body functions and cause acute, progressive, or permanent disabilities. The tolerable UL is the highest level of chronic nutrient intake (usually daily) that is unlikely to pose a risk of adverse health effects for most of the population. Data on the adverse effects of large amounts of many nutrients are unavailable or too limited to establish a UL. Therefore, the lack of a UL does *not* mean that the risk of adverse effects from high intake is nonexistent. Healthy individuals derive no established benefit from consuming nutrient levels above the RDA or AI. Nutrients in commonly eaten foods rarely exceed the UL. However, highly fortified foods and dietary supplements provide more concentrated amounts of nutrients per serving and, thus, pose a potential risk of toxicity. Nutrient supplements are labeled with supplement facts that express the amount of nutrient in absolute units or as the percent of the DV provided per recommended serving size. Total nutrient consumption, including foods; supplements; and over-the-counter medications, such as antacids, should not exceed RDA levels.

Unit 16: Gastroesophageal Reflux Disease (GERD)

Reading 1

Gastroesophageal reflux disease, or GERD, is a digestive disorder that affects the lower esophageal sphincter (LES), the ring of muscle between the esophagus and stomach. Many people, including pregnant women, suffer from heartburn or acid indigestion caused by GERD. Doctors believe that some people suffer from GERD due to a condition called hiatal hernia. In most cases, heartburn can be relieved through diet and lifestyle changes; however, some people may require medication or surgery.



What Is Gastroesophageal Reflux?

Gastroesophageal refers to the stomach and esophagus. Reflux means to flow back or return. Therefore, gastroesophageal reflux is the return of the stomach's contents back up into the esophagus.

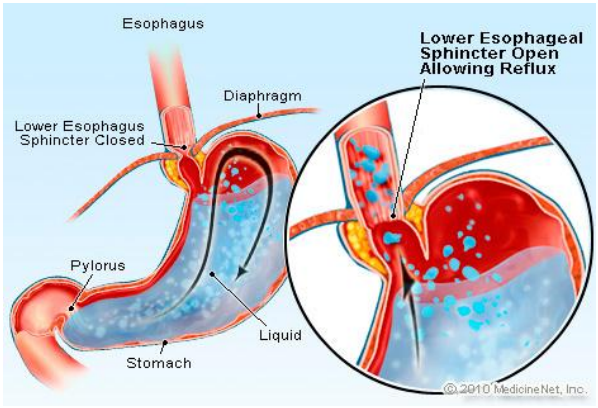
In normal digestion, the lower esophageal sphincter (LES) opens to allow food to pass into the stomach and closes to prevent food and acidic stomach juices from flowing back into the esophagus. Gastroesophageal reflux occurs when the LES is weak or relaxes inappropriately, allowing the stomach's contents to flow up into the esophagus.

The severity of GERD depends on LES dysfunction as well as the type and amount of fluid brought up from the stomach and the neutralizing effect of saliva.

What Is the Role of Hiatal Hernia in GERD?

Some doctors believe a hiatal hernia may weaken the LES and increase the risk for gastroesophageal reflux. Hiatal hernia occurs when the upper part of the stomach moves up into the chest through a small opening in the diaphragm (diaphragmatic hiatus). The diaphragm is the muscle separating the abdomen from the chest. Recent studies show that the opening in the diaphragm helps the support lower end of the esophagus. Many people with a hiatal hernia will not have problems with heartburn or reflux. But having a hiatal hernia may allow stomach contents to reflux more easily into the esophagus.

Coughing, vomiting, straining, or sudden physical exertion can cause increased pressure in the abdomen resulting in hiatal hernia. Obesity and pregnancy also contribute to this condition. Many otherwise healthy people age 50 and over have a small hiatal hernia. Although considered a condition of middle age, hiatal hernias affect people of all ages.

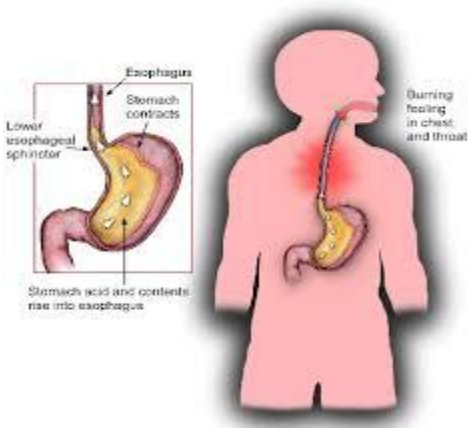


Hiatal hernias usually do not require treatment. However, treatment may be necessary if the hernia is in danger of becoming strangulated (twisted in a way that

cuts off blood supply, called a paraesophageal hernia) or is complicated by severe GERD or esophagitis (inflammation of the esophagus). The doctor may perform surgery to reduce the size of the hernia or to prevent strangulation.

What Other Factors Contribute to GERD?

Dietary and lifestyle choices may contribute to GERD. Certain foods and beverages, including chocolate, peppermint, fried or fatty foods, coffee, or alcoholic beverages, may trigger reflux and heartburn. Studies show that cigarette smoking relaxes the LES. Obesity and pregnancy can also play a role in GERD symptoms.



What Are the Symptoms of Heartburn?

Heartburn, also called acid indigestion, is the most common symptom of GERD and usually feels like a burning chest pain beginning behind the breastbone and moving upward to the neck and throat. Many people say it feels like food is coming back into the mouth leaving an acid or bitter taste.

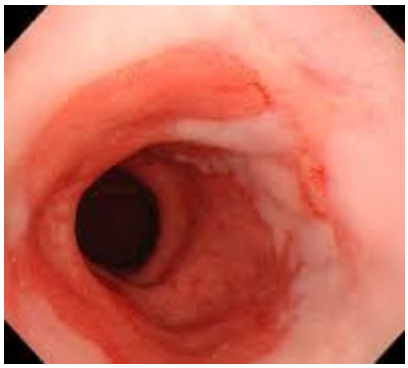
The burning, pressure, or pain of heartburn can last as long as 2 hours and is often worse after eating. Lying down or bending over can also result in heartburn. Many people obtain relief by standing upright or by taking an antacid that clears acid out of the esophagus.

Heartburn pain can be mistaken for the pain associated with heart disease or a heart attack, but there are differences. Exercise may aggravate pain resulting from heart disease, and rest may relieve the pain. Heartburn pain is less likely to be associated with physical activity.

Reading 2

How Common Is Heartburn and GERD?

More than 60 million American adults experience heartburn at least once a month, and more than 15 million adults suffer daily from heartburn. Many pregnant women experience daily heartburn. Recent studies show that GERD in infants and children is more common than previously recognized and may produce recurrent vomiting, coughing, and other respiratory problems.



What Is the Treatment for GERD?

Doctors recommend lifestyle and dietary changes for most people needing treatment for GERD. Treatment aims at decreasing the amount of reflux or reducing damage to the lining of the esophagus from refluxed materials.

Avoiding foods and beverages that can weaken the LES is often recommended. These foods include chocolate, peppermint, fatty foods, coffee, and alcoholic beverages. Foods and beverages that can irritate a damaged esophageal lining, such as citrus fruits and juices, tomato products, and

pepper, should also be avoided if they cause symptoms.

Decreasing the size of portions at mealtime may also help control symptoms. Eating meals at least 2 to 3 hours before bedtime may lessen reflux by allowing the acid in the stomach to decrease and the stomach to empty partially. In addition, being overweight often worsens symptoms. Many overweight people find relief when they lose weight.

Cigarette smoking weakens the LES. Stopping smoking is important to reduce GERD symptoms.

Elevating the head of the bed on 6-inch blocks or sleeping on a specially designed wedge reduces heartburn by allowing gravity to minimize reflux of stomach contents into the esophagus. Do not use pillows to prop yourself up; that only increases pressure on the stomach.

Along with lifestyle and diet changes, your doctor may recommend over-the-counter or prescription treatments.

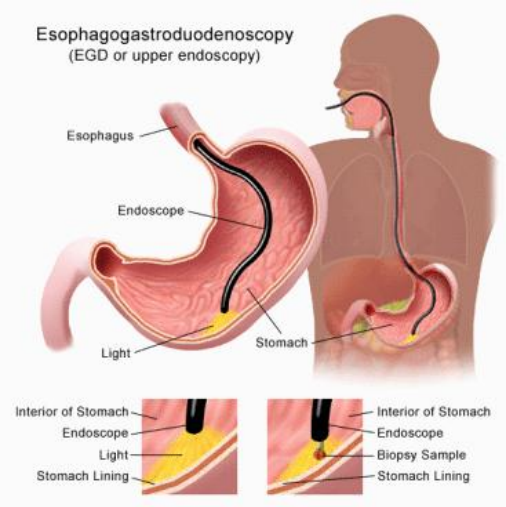
Antacids can help neutralize acid in the esophagus and stomach and stop heartburn. Many people find that nonprescription antacids provide temporary or partial relief. An antacid combined with a foaming agent helps some people. These compounds are believed to form a foam barrier on top of the stomach that prevents acid reflux from occurring.

Long-term use of antacids, however, can result in side effects, including diarrhea, altered calcium metabolism (a change in the way the body breaks down and uses calcium), and buildup of magnesium in the body. Too much magnesium can be serious for patients with kidney disease. If antacids are needed for more than 2 weeks, a doctor should be consulted.

What If Heartburn or GERD Symptoms Persist?

People with severe, chronic esophageal reflux or with symptoms not relieved by the treatments described above may need more complete diagnostic evaluation. Doctors use a variety of tests and procedures to examine a patient with chronic heartburn.

An upper GI series may be performed during the early phase of testing. This test is a special X-ray that shows the esophagus, stomach, and duodenum (the upper part of the small intestine). While an upper GI series provides limited information about possible reflux, it is used to help rule out other diagnoses, such as peptic ulcers.



Endoscopy is an important procedure for individuals with chronic GERD. By placing a small lighted tube with a tiny video camera on the end (endoscope) into the esophagus, the doctor may see inflammation or irritation of the tissue lining the esophagus (esophagitis). If the findings of the endoscopy are abnormal or questionable, biopsy (removing a small sample of tissue) from the lining of the esophagus may be helpful.

Esophageal manometric and impedance studies -- pressure measurements of the esophagus -- occasionally help identify low pressure in the LES or abnormalities in esophageal muscle contraction.

For patients in whom diagnosis is difficult, doctors may measure the acid levels inside ccxthe esophagus through pH testing. Testing pH monitors the acidity level of the esophagus and symptoms during meals, activity, and sleep. Newer techniques of long-term pH monitoring are improving diagnostic capability in this area.

The End!