23 - Special Subjects

Chapter 341. General Principles of Medical Genetics

Introduction

A gene, the basic unit of heredity, is a segment of DNA containing all the information necessary to synthesize a polypeptide (protein). Protein synthesis determines much of the body's structure and function.

Structure

Humans have about 20,000 genes. Genes are contained in chromosomes in the cell nucleus and mitochondria. In humans, somatic (nongerm) cell nuclei, with certain exceptions (eg, RBCs), normally have 46 chromosomes in 23 pairs. Each pair consists of one chromosome from the mother and one from the father. Twenty-two of the pairs, the autosomes, are usually homologous (identical in size, shape, and position and number of genes). The 23rd pair, the sex chromosomes (X and Y), determines a person's sex. Women have 2 X chromosomes (which are homologous) in somatic cell nuclei; men have one X and one Y chromosome (which are heterologous). The X chromosome carries genes responsible for many hereditary traits; the small, differently shaped Y chromosome carries genes that initiate male sex differentiation, as well as a few other genes. Because the X chromosome has many more genes than the Y chromosome, many X chromosome genes in males are not paired. A karyotype is the full set of chromosomes in a person's cells.

Germ cells (egg and sperm) undergo meiosis, which reduces the number of chromosomes to 23—half the number in somatic cells. In meiosis, the genetic information inherited from a person's mother and father is recombined through crossing over (exchange between homologous chromosomes). When an egg is fertilized by a sperm at conception, the normal number of 46 chromosomes is reconstituted.

Genes are arranged linearly along the DNA of chromosomes. Each gene has a specific location (locus), which is typically the same on each of the 2 homologous chromosomes. The genes that occupy the same locus on each chromosome of a pair (one inherited from the mother and one from the father) are called alleles. Each gene consists of a specific DNA sequence; 2 alleles may have slightly different or the same DNA sequences. Having a pair of identical alleles for a particular gene is homozygosity; having a pair of nonidentical alleles is heterozygosity.

Gene Function

Genes consist of DNA. The length of the gene depends on the length of the protein the gene codes for. DNA is a double helix in which nucleotides (bases) are paired; adenine (A) is paired with thymine (T) and guanine (G) is paired with cytosine (C). DNA is transcribed during protein synthesis. When DNA replicates itself during cell division, one strand of DNA is used as a template against which messenger RNA (mRNA) is made. RNA has the same base pairs as DNA, except that uracil (U) replaces thymine (T). Parts of mRNA travel from the nucleus to the cytoplasm and then to the ribosome, where protein synthesis occurs. Transfer RNA (tRNA) brings each amino acid back to the ribosome where it is added to the growing polypeptide chain in a sequence determined by the mRNA. As a chain of amino acids is assembled, it folds upon itself to create a complex 3-dimensional structure under the influence of nearby chaperone molecules.

The code in DNA is written in triplets of the 4 possible nucleotides. Specific amino acids are coded by specific triplets. Because there are 4 nucleotides, the number of possible triplets is 4^3 (64). Because there are only 20 amino acids, there are extra triplet combinations. Some triplets code for the same amino acids as other triplets. Other triplets may code for things such as instructions to start or stop protein synthesis and the order in which to combine and assemble amino acids.

Genes consist of exons and introns. Exons code for amino acid components of the final protein. Introns contain other information that affects control and speed of protein production. Exons and introns together

are transcribed onto mRNA, but the segments transcribed from introns are later spliced out. Transcription is also controlled by antisense RNA, which is synthesized from the DNA strand that is not transcribed into mRNA. Chromosomes consist of histones and other proteins that affect gene expression (which proteins and how many proteins are synthesized from a given gene).

Genotype refers to genetic composition; it determines which proteins are coded for production. Phenotype refers to the entire physical, biochemical, and physiologic makeup of a person—ie, how the cell (and thus the body) functions. Phenotype is determined by the types and amounts of proteins actually synthesized, ie, how the genes are actually expressed. Gene expression depends on factors such as whether a trait is dominant or recessive, the penetrance and expressivity of the gene (see p. 3377), degree of tissue differentiation (determined by tissue type and age), environmental factors, unknown factors, and whether expression is sex-limited or subject to chromosomal inactivation or genomic imprinting. Factors that affect gene expression without changing the genome are epigenetic factors.

Knowledge of the biochemical mechanisms that mediate gene expression is growing rapidly. One mechanism is variability in intron splicing (also called alternative splicing). Because introns are spliced out, the exons may also be spliced out, and then the exons can be assembled in many combinations, resulting in many different mRNAs capable of coding for similar but different proteins. The number of proteins that can be synthesized by humans is > 100,000 even though the human genome has only about 20,000 genes. Other mechanisms mediating gene expression include DNA methylation and histone reactions such as methylation and acetylation. DNA methylation tends to silence a gene. Histones resemble spools around which DNA winds. Histone modifications such as methylation can increase or decrease the quantity of proteins synthesized from a particular gene. Histone acetylation is associated with decreased gene expression. The strand of DNA that is not transcribed to form mRNA may also be used as a template for synthesis of RNA that controls transcription of the opposite strand.

Traits and Inheritance Patterns

A trait may be as simple as the color of the eyes or as complex as susceptibility to diabetes. Expression of a trait may involve one gene or many genes. Some single-gene defects cause abnormalities in multiple tissues, an effect called pleiotropy. For example, osteogenesis imperfecta (a connective tissue disorder that often results from abnormalities in a single collagen gene) may cause fragile bones, deafness, blue-colored sclerae, dys-plastic teeth, hypermobile joints, and heart valve abnormalities (see also p. 2911).

Construction of a family pedigree: The family pedigree (family tree) can be used to diagram inheritance patterns. It is also commonly used in genetic counseling. The pedigree uses conventional symbols to represent family members and pertinent health information about them (see Fig. 341-1). Some familial disorders with identical phenotypes have several patterns of inheritance.

Single-Gene Defects

Genetic disorders determined by a single gene (Mendelian disorders) are easiest to analyze and the most well understood. If expression of a trait requires only one copy of a gene (one allele), that trait is considered dominant. If expression of a trait requires 2 copies of a gene (2 alleles), that trait is considered recessive. An exception is X-linked disorders. Because males usually have no paired allele to offset the effects of most alleles on the X chromosome, the X chromosome allele is expressed in males even if the trait is recessive.

Many specific disorders have been described (see Table 341-1).

Autosomal Dominant

Only one abnormal allele of a gene is needed to express an autosomal dominant trait; ie, heterozygotes and homozygotes for the abnormal gene are affected. A typical pedigree of an autosomal dominant trait is shown in Fig. 341-2.

In general, the following rules apply:

- An affected person has an affected parent.
- A heterozygous affected parent and an unaffected parent have, on average, an equal number of affected and unaffected children; ie, risk of occurrence for each child of an affected parent is 50%.
- Unaffected children of an affected parent do not transmit the trait to their descendents.
- Males and females are equally likely to be affected.

[**Fig. 341-1.** Symbols for constructing a family pedigree.]

[**Table 341-1.** Examples of Genetic Disorders with Mendelian Inheritance]

Autosomal Recessive

Two copies of an abnormal allele are needed to express an autosomal recessive trait. An example of a pedigree is shown in
Fig. 341-3.

In general, the following rules of inheritance apply:

- If normal parents have an affected child, both parents are heterozygotes. On average, one fourth of their children are affected, half are heterozygotes, and one fourth are normal. Therefore, among the children, the chance of not developing the disorder (that is, of being normal or a carrier) is three fourths, and among the unaffected children, the chance of being a carrier is two thirds.
- All children of an affected parent and a genotypically normal parent are phenotypically normal heterozygotes.
- On average, half the children of an affected parent and a heterozygote are affected, and half are heterozygotes.
- All children of 2 affected parents are affected.
- Males and females are equally likely to be affected.
- Heterozygotes are phenotypically normal but carry the abnormal gene.

Relatives are more likely to carry the same mutant allele, so mating between close relatives (consanguinity) increases the likelihood of having affected children. In parent-child or brother-sister unions (incest), the risk of having abnormal children is increased because so much of their genetic material is the same. In certain populations, the percentage of heterozygotes (carriers) is high because of a founder effect (ie, the group started with few members, one of whom was a carrier) or because carriers have a selective advantage (eg, heterozygosity for sickle cell anemia protects against malaria).

[**Fig. 341-2.** Autosomal dominant inheritance.]

If the trait results in a defect of a specific protein (eg, an enzyme), heterozygotes usually have a reduced amount of that protein. If the mutation is known, molecular genetic techniques can identify heterozygous pheno-typically normal people (eg, those with cystic fibrosis most of the time).

X-Linked Dominant

X-linked dominant traits are carried on the X chromosome. Most are rare. Usually, males are more severely affected; some X-linked dominant disorders are often lethal in males. Females who carry only one abnormal allele are affected, but less severely. A typical pedigree is shown in

Fig. 341-4.

In general, the following rules of inheritance apply:

• Affected males transmit the trait to all of their daughters but to none of their sons.

• Affected heterozygous females transmit the trait to half of their children, regardless of sex.

• Affected homozygous females transmit the trait to all of their children.

• Because females can be heterozygous or homozygous, more females have the trait than males. The difference between the sexes is even larger if the disorder is lethal in males.

X-linked dominant inheritance may be difficult to differentiate from autosomal dominant inheritance by studying only inheritance patterns. Large pedigrees are required, with

[**Fig. 341-3.** Autosomal recessive inheritance.]

[**Fig. 341-4.** X-linked dominant inheritance.]

particular attention to children of affected males because male-to-male transmission rules out X-linkage (males pass only their Y chromosomes to their sons).

X-Linked Recessive

X-linked recessive traits are carried on the X chromosome. Thus, nearly all affected people are male because most females have one normal copy of the involved gene (ie, they are heterozygous). A typical pedigree is shown in
Fig. 341-5.

In general, the following rules of inheritance apply:

• Nearly all affected people are male.

• Heterozygous females are usually pheno-typically normal but, as carriers, transmit the abnormal gene to half of their children.

• Half the sons of a carrier female are affected, and half the daughters are carriers.

• An affected male never transmits the trait to his sons.

• All daughters of an affected male are carriers.

• No daughters of a carrier female and a normal father are affected, but half are carriers.

Occasionally, females who are heterozygous for X-linked mutations show some expression, but they are rarely affected as severely as affected males.

Factors Affecting Gene Expression

Many factors can affect gene expression. Some cause the expression of traits to deviate from the patterns predicted by Mendelian inheritance.

Penetrance and expressivity: Penetrance is how often a gene is expressed. It is defined as the percentage of people who have the gene and who develop the corresponding pheno-type (see Fig. 341-6). A gene with incomplete (low) penetrance may not be expressed even when the trait is dominant or when it is recessive and the gene responsible for that trait is present on both chromosomes. Penetrance of the same gene may vary from person to person and may depend on a person's age. Even

when an abnormal allele is not expressed (nonpenetrance), the unaffected carrier of the abnormal allele can pass it to children, who may have the clinical abnormality. In such cases, the pedigree appears to skip a generation. However, some cases of apparent nonpenetrance are due to the examiner's unfamiliarity with or inability to recognize minor manifestations of the disorder. Patients with minimal expression are sometimes considered to have a forme fruste of the disorder.

[Fig. 341-5. X-linked recessive inheritance.]

Expressivity is the extent to which a gene is expressed in one person. It can be graded as a percentage; eg, when a gene has 50% expressivity, only half the features are present or the severity is only half of what can occur with full expression. Expressivity may be influenced by the environment and by other genes, so people with the same gene may vary in phenotype. Expressivity can vary even among members of the same family.

Sex-limited inheritance: A trait that appears in only one sex is called sex-limited. Sex-limited inheritance is distinct from X-linked inheritance, which refers to traits carried on the X chromosome. Sex-limited inheritance, perhaps more correctly called sex-influenced inheritance, refers to special cases in which sex hormones and other physiologic differences between males and females alter the expressivity and penetrance of a gene. For example, premature baldness (known as male-pattern baldness) is an autosomal dominant trait, but such baldness is rarely expressed in females and then usually only after menopause.

Genomic imprinting: Genomic imprinting is the differential expression of genetic material depending on whether it has been inherited from the father or mother. For most

[Fig. 341-6. Penetrance and expressivity.]

autosomes, both the parental and maternal alleles are expressed. However, in < 1% of alleles, expression is possible only from the paternal or maternal allele. For example, expression of the gene for insulin-like growth factor 2 is normally expressed only from the paternal allele. Genomic imprinting is usually determined by effects that occur normally in the development of gametes. Changes such as methylation of DNA may cause certain maternal or paternal alleles to be expressed to different degrees. A disorder may appear to skip a generation if genomic imprinting prevents the causative allele from being expressed. Defective imprinting, such as abnormal activation or silencing of alleles, can result in disorders (eg, Prader-Willi syndrome, Angelman syndrome).

Codominance: Codominant alleles are both observed. Thus, the phenotype of heterozygotes is distinct from that of either homozygote. For example, if a person has one allele coding for blood type A and one allele coding for blood type B, the person has both blood types (blood type AB).

Chromosomal inactivation: In females, who have more than one X chromosome (except in eggs), all but one of the X chromosomes is inactivated; ie, most of the alleles on that chromosome are not expressed. Inactivation occurs individually in each cell early in fetal life; sometimes it is the X from the mother that is inactivated, and sometimes it is the X from the father. Sometimes most of the X chromosome inactivation comes from one parent—called skewed X inactivation. Either way, once inactivation has taken place in a cell, all descendants of that cell have the same X inactivation.

However, some alleles on the inactive X chromosome do express. Many of these alleles are on chromosomal regions corresponding to regions of the Y chromosomes (and are thus called pseudoautosomal regions, because both males and females receive 2 copies of these regions).

Multifactorial (Complex) Inheritance

Expression of many traits may involve multiple genes. Many such traits (eg, height) are distributed along a bell-shaped curve (normal distribution). Normally, each gene adds to or subtracts from the trait independently of other genes. In this distribution, few people are at the extremes and many are in the middle because people are unlikely to inherit multiple factors acting in the same direction. Environmental factors also add to or subtract from the final result.

Many relatively common congenital anomalies and familial disorders result from multifactorial inheritance. In an affected person, the disorder represents the sum of genetic and environmental influences. Risk of the occurrence of such a trait is much higher in 1st-degree relatives (siblings, parents, or children who share, on average, 50% of the affected person's genes) than in more distant relatives, who are likely to have inherited only a few high-liability genes.

Common disorders with multifactorial inheritance include hypertension, coronary artery disease, diabetes mellitus, cancer, cleft palate, and arthritis. Many specific genes contributing to these traits are being identified. Genetically determined predisposing factors, including a family history and specific biochemical pathways often identified by molecular markers (eg, high cholesterol), can sometimes identify people who are at risk and are likely to benefit from preventive measures.

Multigenic, multifactorial traits seldom produce clear patterns of inheritance; however, these traits tend to occur more often among certain ethnic and geographic groups or among one sex or the other.

Unusual Aspects of Inheritance

Certain situations represent aberrant inheritance, often because genes or chromosomes are altered. However, some of these alterations, such as mosaicism, are very common; others, such as polymorphisms, are so common that they may be considered normal variants.

Mutations and polymorphisms: Variations in DNA can occur spontaneously or in response to cellular insults (eg, radiation, mutagenic drugs, viruses). Some are repaired by the cell's DNA error correction mechanisms. Others are not and can be passed on to subsequently replicated cells; in such cases, the variation is termed a mutation. However, offspring can inherit the mutation only if germ cells are affected. Mutations may be unique to an individual or family. Most mutations are rare. Polymorphisms begin as mutations. They are variations in DNA that have become common in a population (prevalence of ≥ 1%) through sufficient propagation or other mechanisms. Most are stable and inconsequential. A common example is human blood groups (A, B, AB, and O).

Mutations (and polymorphisms) involve random changes in DNA. Most have little effect on cell function. Some change cell function, usually in a detrimental way, and some are lethal to the cell. Examples of detrimental changes in cell function are mutations that cause cancer by creating oncogenes or altering tumor suppressor genes (see p. 1047). Rarely, a change in cell function confers a survival advantage. These mutations are more likely to be propagated. The mutation causing sickle cell anemia confers resistance to malaria. This resistance conferred a survival advantage in areas where malaria was endemic and often fatal. However, by causing symptoms and complications of sickle cell anemia, the mutation also has harmful effects usually when present in the homozygous state.

When and in what cell type mutations occur can explain certain abnormalities in inheritance patterns. Typically, an autosomal dominant disorder is expected to be present in one or both parents of an affected person. However, some disorders with autosomal dominant inheritance can appear de novo (in people whose parents have a normal phenotype). For example, about 80% of people with achondroplastic dwarfism have no family history of dwarfism and thus represent new (de novo) mutations. In many of these people, the mechanism is a spontaneous mutation occurring early in their embryonic life. Thus, other off-spring have no increased risk of the disorder. However, in some of them, the disorder develops because of a germ cell mutation in their parents (eg, an autosomal dominant gene in a phenotypically normal parent). If so, other offspring have an increased risk of inheriting the mutation.

Mosaicism: Mosaicism occurs when a person starting from a single fertilized egg develops ≥ 2 cell lines differing in genotype. Mosaicism is a normal consequence of X inactivation in females (see p. 3378); in most females, some cells have an inactive maternal X, and other cells have an inactive paternal X. Mosaicism can also result from mutations. Mutations are likely to occur during cell division in any large multicellular organism; each time a cell divides, 4 or 5 changes are estimated to occur in the DNA. Because these changes can be passed on to subsequently produced cells, large multicellular organisms have subclones of cells that have slightly different genotypes.

Mosaicism may be recognized as the cause of disorders in which patchy changes occur. For example, McCune-Albright syndrome is associated with patchy dysplastic changes in the bone, endocrine gland abnormalities, patchy pigmentary changes, and occasionally heart or liver abnormalities. Occurrence of the McCune-Albright mutation in all cells would cause early death; however, people with mosaicism survive because normal tissue supports the abnormal tissue. Occasionally, a parent with a single-gene disorder seems to have a mild form but actually represents a mosaic; the parent's offspring is more severely affected if they receive a germ cell with the mutant allele and thus have the abnormality in every cell.

Chromosomal abnormalities are most often fatal to the fetus. However, chromosomal mosaicism occurs in some embryos, resulting in some chromosomally normal cells, which can allow offspring to be born alive. Chromosomal mosaicism can be detected with prenatal genetic testing, particularly chorionic villus sampling.

Extra or missing chromosomes: Abnormal numbers of autosomes usually result in severe abnormalities. For example, extra autosomes typically cause abnormalities such as Down syndrome and other severe syndromes or can be fatal to the fetus. Absence of an autosome is always fatal to the fetus. Chromosomal abnormalities (see p. 2997) can usually be diagnosed before birth.

Because of X chromosomal inactivation, having an abnormal number of X chromosomes is usually much less severe than having an abnormal number of autosomes. For example, the abnormalities resulting from the absence of one X chromosome are usually relatively minor (eg, in Turner's syndrome, see p. 3003). Also, females with 3 X chromosomes (triple X syndrome, see p. 3005) are often physically and mentally normal; only one X chromosome of genetic material is fully active even if a female has > 2 X chromosomes (the extra X chromosomes are also partly inactivated).

Uniparental disomy: Uniparental disomy occurs when both chromosomes have been inherited from only one parent. It is very rare and is thought to involve trisomy rescue; ie, the zygote started off as a trisomy (having 3 instead of 2 of a particular chromosome) and one of the 3 was lost, a process that leads to uniparental disomy when the 2 chromosomes that remain are from the same parent (in about one third of cases). Uniparental disomy may cause abnormal inheritance patterns. For example, if duplicates of the same chromosome (isodisomy) are present and carry an abnormal allele for an autosomal recessive disorder, affected people can have an autosomal recessive disorder even though only one parent is a carrier.

Chromosomal translocation: Chromosomal translocation is exchange of chromosomal parts between nonpaired (nonhomologous) chromosomes. If chromosomes exchange equal parts of genetic material, the translocation is described as balanced. Unbalanced translocations result in loss of chromosomal material, usually the short arms of 2 fused chromosomes, leaving only 45 chromosomes remaining. Most people with translocations are phenotypically normal. However, translocations may cause or contribute to leukemia (acute myelocytic leukemia [AML] or chronic myelocytic leukemia [CML]) or Down syndrome. Translocations may increase risk of chromosomal abnormalities in offspring, particularly unbalanced translocations. Because chromosomal abnormalities are often fatal to an embryo or a fetus, a parental translocation may result in unexplained recurrent spontaneous abortions or infertility.

Triplet (trinucleotide) repeat disorders: A triplet repeat disorder results when a triplet of nucleotides is repeated an abnormal number of times within a gene. The number of triplets may increase when the gene is transmitted from one generation to the next or as cells divide within the body. When triplets increase enough, genes stop functioning normally. Triplet repeat disorders are infrequent but cause several neurologic disorders (eg, myotonic dystrophy, fragile X mental retardation), particularly those involving the CNS (eg, Huntington's disease). Triplet repeat disorders can be detected by techniques that analyze DNA.

Anticipation: Anticipation occurs when a disorder has an earlier age of onset and is expressed more severely in each successive generation. Anticipation may occur when a parent is a mosaic and the child has the full mutation in all cells. It may also occur in triplet repeat disorders when the number of repeats and thus the severity of gene dysfunction increase with each generation.

Mitochondrial DNA Abnormalities

Each cell has several hundred mitochondria in its cytoplasm. Mitochondria contain DNA in a single circular chromosome that codes for 13 proteins, various RNAs, and several regulating enzymes. However, > 90% of mitochondrial proteins are coded by nuclear genes. For practical purposes, all mitochondria are inherited from the cytoplasm of the egg; thus, mitochondrial DNA comes only from the mother.

Mitochondrial disorders (see also p. 3023) can be due to mitochondrial or nuclear DNA abnormalities (eg, deletions, duplications, mutations). High-energy tissues (eg, muscle, heart, brain) are particularly at risk of malfunction due to mitochondrial abnormalities. Particular mitochondrial DNA abnormalities result in characteristic manifestations (see Table 341-2). Mitochondrial disorders are equally common among males and females.

Mitochondrial abnormalities may occur in many common disorders such as some types of Parkinson's disease (which may involve large mitochondrial deletions in the cells of the basal ganglia) and many types of muscle disorders.

Maternal inheritance patterns characterize abnormalities of mitochondrial DNA. Thus, all offspring of an affected female are at risk of inheriting the abnormality, but no offspring of an affected male are at risk. Variability in clinical manifestations is the rule and may be due in part to variable mixtures of inherited mutant and normal mitochondrial genomes within cells and tissues.

Genetic Diagnostic Technologies

Genetic diagnostic technology is rapidly improving. DNA or RNA can be amplified, producing many copies of a gene or gene segment, using PCR.

Gene probes can be used to locate specific segments of normal or mutated DNA. A known DNA segment may be cloned and then radioactively or fluorescently tagged; this segment is then combined with a test specimen. The tagged DNA binds to its complementary DNA segment and can be detected by measuring the radioactivity or the amount and type of fluorescence. Gene probes can detect a number of disorders before and after birth. In the future, gene probes will probably be used to test people for many major genetic disorders simultaneously.

[**Table 341-2.** Mitochondrial Disorders]

Microchips are powerful new tools that can be used to identify DNA mutations, pieces of RNA, or proteins. A single chip can test for 30,000 different DNA changes using only one sample.

Clinical Uses of Genetics

Disease Understanding

Genetics has advanced understanding of many disorders, sometimes allowing them to be reclassified. For example, classification of many spinocerebellar ataxias has been changed from one based on clinical criteria to one based on genetic criteria (see p. 1778). The Online Mendelian Inheritance in Man (OMIM) database is a searchable catalog of human genes and genetic disorders.

Diagnosis

Genetic testing is used to diagnose many disorders (eg, Turner's syndrome, Klinefelter's syndrome, hemochromatosis). Diagnosis of a genetic disorder often indicates that relatives of the affected person should be screened for the genetic defect or for carrier status.

Genetic Screening

Genetic screening may be indicated in populations at risk of a particular genetic disorder. The usual criteria for genetic screening are

• Genetic inheritance patterns are known.

• Effective therapy is available.

• Screening tests are sufficiently valid, reliable, sensitive and specific, noninvasive, and safe.

Prevalence in a defined population must be high enough to justify the cost of screening.

One aim of prenatal genetic screening (see p. 2598) is to identify asymptomatic parental heterozygotes carrying a gene for a recessive disorder. For example, Ashkenazi Jews are screened for Tay-Sachs disease, blacks are screened for sickle cell anemia, and several ethnic groups are screened for thalassemia (see Table 259-1 on p. 2600). If a heterozygote's mate is also a heterozygote, the couple is at risk of having an affected child. If the risk is high enough, prenatal diagnosis can be pursued (eg, with amniocentesis, chorionic villus sampling, umbilical cord blood sampling, maternal blood sampling, or fetal imaging). In some cases, genetic disorders diagnosed prenatally can be treated, preventing complications. For instance, special diet or replacement therapy can minimize or eliminate the effects of phenylketonuria, galactosemia, and hypothyroidism. Corticosteroids given to the mother before birth may decrease the severity of congenital virilizing adrenal hypoplasia.

Screening may be appropriate for people with a family history of a dominantly inherited disorder that manifests later in life, such as Huntington's disease or cancers associated with abnormalities of the *BRCA1* or *BRCA2* genes. Screening clarifies the risk of developing the condition for that person, who can then make appropriate plans, such as for more frequent screening or preventive therapy.

Screening may also be indicated when a family member is diagnosed with a genetic disorder. A person who is identified as a carrier can make informed decisions about reproduction.

Treatment

Understanding the genetic and molecular basis of disorders may help guide therapy. For example, dietary restriction can eliminate compounds toxic to patients with certain genetic defects, such as phenylketonuria or homocystinuria. Vitamins or other agents can modify a biochemical pathway and thus reduce toxic levels of a compound; eg, folate (folic acid) reduces homocysteine levels in people with 5,10-methylene tetrahydrofolate reductase polymorphism. Therapy may involve replacing a deficient compound or blocking an overactive pathway.

Pharmacogenomics: Pharmacogenomics is the science of how genetic characteristics affect the response to drugs. One aspect of pharmacogenomics is how genes affect pharmacokinetics. Genetic characteristics of a person may help predict response to treatments. For example, metabolism of warfarin is determined partly by variants in genes for the CYP2C9 enzyme and for the vitamin K epoxide reductase complex protein 1. Genetic variations (eg, in production of UDP [uridine diphosphate]-glucoronosyltransferase 1A1) also help predict whether the anticancer drug irinotecan will have intolerable adverse effects.

Another aspect of pharmacogenomics is pharmacodynamics (how drugs interact with cell receptors—see p. 3181). Genetic and thus receptor characteristics of disordered tissue can help provide more precise targets when developing drugs (eg, anticancer drugs). For example, trastuzumab can target specific cancer cell receptors in metastatic breast cancers that amplify the *HER2/neu* gene. Presence of the Philadelphia chromosome in patients with chronic myelocytic leukemia (CML) helps guide chemotherapy.

Gene therapy: Gene therapy can broadly be considered any treatment that changes gene function. However, gene therapy is often considered specifically the insertion of normal genes into the cells of a person who lacks such normal genes because of a specific genetic disorder. The normal genes can be manufactured, using PCR, from normal DNA donated by another person. Because most genetic disorders are recessive, usually a dominant normal gene is inserted. Currently, such insertion gene therapy is most likely to be effective in the prevention or cure of single-gene defects, such as cystic fibrosis.

One way to transfer DNA into host cells is by viral transfection. The normal DNA is inserted into a virus, which then transfects the host cells, thereby transmitting the DNA into the cell nucleus. Some important concerns about insertion using a virus include reactions to the virus, rapid loss of (failure to propagate) the new normal DNA, and damage to the virus by antibodies developed against the transfected protein, which the immune system recognizes as foreign. Another way to transfer DNA uses liposomes, which are absorbed by the host cells and thereby deliver their DNA to the cell nucleus. Potential problems with liposome insertion methods include failure to absorb the liposomes into the cells, rapid degradation of the new normal DNA, and rapid loss of integration of the DNA.

With antisense technology, rather than inserting normal genes, gene expression can be altered; eg, drugs can combine with specific parts of the DNA, preventing or decreasing gene expression. Antisense technology is currently being tried for cancer therapy but is still very experimental. However, it seems to hold more promise than gene insertion therapy because the success rates may be higher and complications may be fewer.

Another approach to gene therapy is to modify gene expression chemically (eg, by modifying DNA methylation). Such methods have been tried experimentally in treating cancer. Chemical modification may also affect genomic imprinting, although this effect is not clear.

Gene therapy is also being studied experimentally in transplantation surgery. Altering the genes of the transplanted organs to make them more compatible with the recipient's genes makes rejection (and thus the need for immunosuppressive drugs) less likely. However, this process works only rarely.

Ethical Controversies

With new genetic diagnostic and therapeutic capabilities come many controversies about how they should be used. For example, there are concerns that genetic information might be used improperly to discriminate (eg, by denying health insurance coverage or employment) against people with genetic risk factors for particular disorders. Issues include the privacy of a person's own genetic information and the question of whether testing should be compulsory.

Prenatal screening for genetic abnormalities that cause serious disorders is widely supported; however, there is concern that screening could also be used to select for traits that are aesthetically desirable (eg, physical appearance, intelligence).

Cloning is highly controversial. Animal studies suggest cloning is much more likely than natural methods to result in defects that are lethal or cause serious health problems. Creating a human by cloning is widely seen as unethical, is usually illegal, and is technically difficult.

Chapter 342. Clinical Decision Making

Introduction

Clinicians must integrate a huge variety of clinical data while facing conflicting pressures to decrease diagnostic uncertainty, risks to patients, and costs. Deciding what information to gather, which tests to order, how to interpret and integrate this information to draw diagnostic conclusions, and which treatments to give is known as clinical decision making.

When presented with a patient, clinicians usually must answer the following questions:

• What disease does this patient have?

• Should this patient be treated?

• Should testing be done?

In straightforward or common situations, clinicians often make such decisions informally; diagnoses are made by recognizing disease patterns, and testing and treatment are initiated based on customary practice. For example, during a flu epidemic, a healthy adult who has had fever, aches, and harsh cough for 2 days is likely to be recognized as another case of influenza and provided only appropriate symptomatic relief. Such pattern recognition is efficient and easy to use but may be subject to error because other diagnostic and therapeutic possibilities are not seriously or systematically considered. For example, a patient with that flu pattern and decreased O_2 saturation might instead have bacterial pneumonia and require antibiotics. In more complex cases, a structured, quantitative, analytical methodology may be a better approach to decision making. Even when pattern recognition provides the most likely diagnostic possibility, analytic decision making is often used to confirm the diagnosis. Analytic methods may include application of the principles of evidence-based medicine, use of clinical guidelines, and use of various specific quantitative techniques (eg, Bayes' theorem).

Evidence-Based Medicine and Clinical Guidelines

Physicians have always felt that their decisions were based on evidence; thus, the current term "evidence-based medicine" is somewhat of a misnomer. However, for many clinicians, the "evidence" is often a vague combination of recollected strategies effective in previous patients, advice given by mentors and colleagues, and a general impression of "what is being done" based on random journal articles, abstracts, symposia, and advertisements. This kind of practice results in wide variations in strategies for diagnosing and managing similar conditions, even when strong evidence exists for favoring one particular strategy over another. Variations exist among different countries, different regions, different hospitals, and even within individual group practices. These variations have led to a call for a more systematic approach to identifying the most appropriate strategy for an individual patient; this approach is called evidence-based medicine (EBM). EBM is built on reviews of relevant medical literature and follows a discrete series of steps.

Evidence-Based Medicine

EBM is not the blind application of advice gleaned from recently published literature to individual patient problems. Rather, EBM requires the use of a series of steps to gather sufficiently useful information to answer a carefully crafted question for an individual patient. Fully integrating the principles of EBM also incorporates the patient's value system, which includes such things as costs incurred, the patient's religious or moral beliefs, and patient autonomy. Applying the principles of EBM typically involves the following steps:

• Formulating a clinical question

• Gathering evidence to answer the question

• Evaluating the quality and validity of the evidence

• Deciding how to apply the evidence to the care of a given patient

Formulating a clinical question: Questions must be specific. Specific questions are most likely to be addressed in the medical literature. A well-designed question specifies the population, intervention (diagnostic test, treatment), comparison (treatment A vs treatment B), and outcome. "What is the best way to evaluate someone with abdominal pain?" is not a good question. A better, more specific question may be "Is CT or ultrasonography preferable for diagnosing acute appendicitis in a 30-yr-old male with acute lower abdominal pain?"

Gathering evidence to answer the question: A broad selection of relevant studies is obtained from a review of the literature. Standard resources are consulted (eg, MEDLINE, the Cochrane Collaboration [treatment options], the National Guideline Clearinghouse, ACP Journal Club).

Evaluating the quality and validity of the evidence: Not all scientific studies are of equal value. Different types of studies have different scientific strengths and legitimacy, and for any given type of study, individual examples often vary in quality of the methodology, internal validity, and generalizability of results (external validity).

Levels of evidence are graded 1 through 5 in decreasing order of quality. Types of studies at each level vary somewhat with the clinical question (eg, of diagnosis, treatment, or economic analysis), but typically level 1 evidence (the highest quality) consists of systematic reviews or meta-analyses of randomized controlled trials and high-quality, single, randomized controlled trials. Level 2 evidence is well-designed cohort studies. Level 3 evidence is case-control studies. Level 4 evidence is case series and poor-quality cohort and case-control studies. Level 5 evidence is expert opinion not based on critical appraisal but is based on reasoning from physiology, bench research, or underlying principles.

For EBM analysis, the highest level of evidence available is selected. Ideally, a significant number of large, well-conducted level 1 studies are available. However, because the number of high-quality, randomized, controlled trials is vanishingly small compared with the number of possible clinical questions, less reliable level 4 or 5 evidence is very often all that is available. Lower-quality evidence does not mean that the EBM process cannot be followed, just that the strength of the conclusion is weaker.

Deciding how to apply the evidence to the care of a given patient: Because the best available evidence may have come from patient populations with different characteristics from those of the patient in question, some judgment is required. Additionally, patients' wishes regarding aggressive or invasive tests and treatment must be taken into account as well as their tolerance for discomfort, risk, and uncertainty. For example, even though an EBM review may definitively show a 3-mo survival advantage from an aggressive chemotherapy regimen in a certain form of cancer, patients may differ on whether they prefer to gain the extra time or avoid the extra discomfort.

Limitations: Dozens of clinical questions are faced during the course of even one day in a busy practice. Although some of them may be the subject of an existing EBM review available for reference, most are not, and preparing an EBM analysis is too time-consuming to be useful in answering an immediate clinical question. Even when time is not a consideration, many clinical questions do not have any relevant studies in the literature.

Clinical Guidelines

Clinical guidelines have become common in the practice of medicine; many specialty societies have published such guidelines. Most well-conceived clinical guidelines are developed using a specified method that incorporates principles of EBM and consensus recommendations made by a panel of experts.

Some clinical guidelines follow "if, then" rules (eg, if a patient is febrile and neutropenic, then institute broad-spectrum antibiotics). More complex, multistep rules may be formalized as algorithms. Guidelines and algorithms are generally straightforward and easy to use but should be applied only to patients

whose clinical characteristics (eg, demographics, comorbidities, clinical features) are similar to those of the patient group used to create the guideline. Furthermore, guidelines do not take into account the degree of uncertainty inherent in test results, the likelihood of treatment success, and the relative risks and benefits of each course of action. To incorporate uncertainty and the value of outcomes into clinical decision making, clinicians must often apply the principles of quantitative or analytical medical decision making.

Clinical Decision-Making Strategies

One of the most commonly used strategies for medical decision making mirrors the scientific method of hypothesis generation followed by hypothesis testing. Diagnostic hypotheses are accepted or rejected based on testing.

Hypothesis generation: Hypothesis generation involves the identification of the main diagnostic possibilities (differential diagnosis) that might account for the patient's clinical problem. The patient's chief complaint (eg, chest pain) and basic demographic data (age, sex, race) are the starting points for the differential diagnosis, which is usually generated by pattern recognition. Each element on the list of possibilities is ideally assigned an estimated probability (see Sidebar 342-1), or likelihood, of its being the correct diagnosis (pre-test probability—see Table 342-1).

Clinicians often use vague terms such as "highly likely," "improbable," and "cannot rule out" to describe the likelihood of disease. Both clinicians and patients often misinterpret such semiquantitative terms; explicit statistical terminology should be used instead when available. Mathematical computations assist clinical decision making and, even when exact numbers are unavailable, can better define clinical probabilities and narrow the list of hypothetical diseases further.

Hypothesis testing: The initial differential diagnosis based on chief complaint and demographics is usually very large, so the clinician first tests the hypothetical possibilities during the history and physical examination, asking questions or doing specific examinations that support or refute a suspected diagnosis. For instance, in a patient with chest pain, a history of leg pain and a swollen, tender leg detected during examination increases the probability of pulmonary embolism.

Sidebar 342-1 Probability and Odds

The **probability** of a disease (or event) occurring in a patient whose clinical information is unknown is the frequency with which that disease or event occurs in a population. Probabilities range from 0.0 (impossible) to 1.0 (certain) and are often expressed as percentages (from 0 to 100). A disease that occurs in 2 of 10 patients has a probability of 2/10 (0.2 or 20%). Rounding very small probabilities to 0, thus excluding all possibility of disease (sometimes done in implicit clinical reasoning), can lead to erroneous conclusions when quantitative methods are used.

Odds represent the ratio of affected to unaffected patients (ie, the ratio of disease to no disease). Thus, a disease that occurs in 2 of 10 patients (probability of 2/10) has odds of 2/8 (0.25, often expressed as 1 to 4). Odds (Ω) and probabilities (p) can be converted one to the other, as in $\Omega = p/(1 - p)$ or $p = \Omega/(1 + \Omega)$.

When the history and physical examination form a clear-cut pattern, a presumptive diagnosis is made. Diagnostic testing is used when uncertainties persist after the history and physical examination, particularly when the diseases remaining under consideration are serious or have dangerous or costly treatment. Test results further modify the probabilities of different diagnoses (post-test probability). For example, Table 342-1 shows how the additional findings that the hypothetical patient had leg pain and swelling and a normal ECG and chest x-ray modify diagnostic probabilities—the probability of acute coronary syndrome, dissecting aneurysm, and pneumothorax decreases, and the probability of pulmonary, embolism increases. These changes in probability may lead to additional testing (in this example, probably chest CT angiography) that further modifies post-test probability (see Table 342-1)

and, in some cases, confirms or refutes a diagnosis.

Probability Estimations and the Treatment Threshold

The disease probability at and above which treatment is given and no further testing is warranted is termed the treatment threshold (TT).

The above hypothetical example of a patient with chest pain converged on a near-certain diagnosis (98% probability). When diagnosis of a disease is certain, the decision to treat is a straightforward determination that there is a benefit of treatment (compared with no treatment and taking into account adverse effects of treatment). When the diagnosis has some degree of uncertainty, as is almost always the case, the decision to treat also must balance the benefit of treating a sick person against the risk of erroneously treating a well person or a person with a different disorder; benefit and risk encompass both financial and medical consequences. This balance must take into account both the likelihood of disease and the magnitude of the benefit and risk. This balance determines where the clinician sets the TT.

Conceptually, if the benefit of treatment is very high and the risk is very low (as when giving a safe antibiotic to a patient with diabetes who possibly has a life-threatening infection), clinicians tend to accept high diagnostic uncertainty and might initiate treatment even if probability of infection is fairly low (eg, 30%—see Fig. 342-1). However, when the risk of treatment is very high (as when doing a pneumonectomy for possible lung cancer), clinicians want to be extremely sure of the diagnosis and might recommend treatment only when the probability of cancer is very high, perhaps > 95% (see Fig. 342-1). Note that the TT does not necessarily correspond to the probability at which a disease might be considered

[**Table 342-1.** Hypothetical Differential Diagnosis and Pre-Test and Post-Test Probabilities for a 50-yr-old Hypertensive, Diabetic Cigarette Smoker with Chest Pain]

[**Fig. 342-1.** Variation of treatment threshold (TT) with risk of treatment.]

confirmed or ruled in. It is simply the point at which the risk of not treating is greater than the risk of treating.

Quantitatively, the TT can be described as the point at which probability of disease (p) times benefit of treating a person with disease (B) equals probability of no disease (1 - p) times risk of treating a person without disease (R). Thus, at the TT

$$p \times B = (1 - p) \times R$$

Solving for p, this equation reduces to

$$p = R/(B + R).$$

From this equation, it is apparent that if B (benefit) and R (risk) are the same, the TT becomes 1/(1 + 1) = 0.5, which means that when the probability of disease is > 50%, clinicians would treat, and when probability is < 50%, clinicians would not treat.

For a clinical example, a patient with chest pain can be considered. How high should the clinical likelihood of acute MI be before thrombolytic therapy should be given, assuming the only risk considered is short-term mortality? If it is postulated (for illustration) that mortality due to intracranial hemorrhage with thrombolytic therapy is 1%, then 1% is R, the fatality rate of mistakenly treating a patient who does not have an MI. If net mortality in patients with MI is decreased by 3% with thrombolytic therapy, then 3% is B. Then, TT is 1/(3 + 1), or 25%; thus, treatment should be given if the probability of acute MI is > 25%.

Alternatively, the TT equation can be rearranged to show that the TT is the point at which the odds of disease p/(1 - p) equal the risk:benefit ratio (R/B). The same numerical result is obtained as in the previously described example, with the TT occurring at the odds of the risk:benefit ratio (1/3); 1/3 odds

corresponds to the previously obtained probability of 25% (see Sidebar 342-1).

Limitations: Quantitative clinical decision making seems precise, but because many elements in the calculations are often imprecisely known (if they are known at all), this methodology is difficult to use in all but the most well-defined and studied clinical situations.

Cognitive Errors in Clinical Decision Making

Although quantitative mathematical models can guide clinical decision making, clinicians rarely use formal computations to make patient care decisions in day-to-day practice. Rather, an intuitive understanding of probabilities is combined with cognitive processes called heuristics to guide clinical judgment. Heuristics are often referred to as rules of thumb, educated guesses, or mental shortcuts. Heuristics usually involve pattern recognition and rely on a subconscious integration of somewhat haphazardly gathered patient data with prior experience rather than on a conscious generation of a rigorous differential diagnosis that is formally evaluated using specific data from the literature.

Such informal reasoning is often fallible because heuristics may cause several types of unconscious errors (cognitive errors). Studies suggest that more medical errors involve cognitive error than lack of knowledge or information.

Types of cognitive error: There are many types of cognitive errors, and although it is obviously more important to avoid errors than to properly classify them once made, being aware of common types of cognitive errors can help clinicians recognize and avoid them.

Cognitive errors may roughly be classified as those involving

• Faulty assessment of pre-test probability (overestimating or underestimating disease likelihood)

• Failure to seriously consider all relevant possibilities

Both types of error can easily lead to improper testing (too much or too little) and missed diagnoses.

Availability error occurs when clinicians misestimate the prior probability of disease because of recent experience. Experience often leads to overestimation of probability when there is memory of a case that was dramatic or that involved a patient who fared poorly or a lawsuit. For example, a clinician who recently missed the diagnosis of pulmonary embolism in a healthy young woman who had vague chest discomfort but no other findings or apparent risk factors might then overestimate the risk in similar patients and become more likely to do chest CT angiography for similar patients despite the very small probability of disease. Experience can also lead to underestimation. For example, a junior resident who has seen only a few patients with chest pain, all of whom turned out to have benign causes, may begin to do cursory evaluations of that complaint even among populations in which disease prevalence is high.

Representation error occurs when clinicians judge the probability of disease based on how closely the patient's findings fit classic manifestations of a disease without taking into account disease prevalence. For example, although several hours of vague chest discomfort in a thin, athletic, healthy-appearing 60-yr-old man who has no known medical problems and who now looks and feels well does not match the typical profile of an MI, it would be unwise to dismiss that possibility because MI is common among men of that age and has highly variable manifestations. Conversely, a 20-yr-old healthy man with sudden onset of severe, sharp chest pain and back pain may be suspected of having a dissecting thoracic aortic aneurysm because those clinical features are common in aortic dissection. The cognitive error is not taking into account the fact that aortic dissections are exceptionally rare in a 20-yr-old, otherwise healthy patient; that disorder can be dismissed out of hand and other, more likely causes (eg, pneumothorax, pleuritis) should be considered. Representation error is also involved when clinicians fail to recognize that positive test results in a population where the tested disease is rare are more likely to be false positive than true positive.

Premature closure is one of the most common errors; clinicians make a quick diagnosis (often based on pattern recognition), fail to consider other possible diagnoses, and stop collecting data (jump to

conclusions); often, even the suspected diagnosis is not confirmed by appropriate testing. Premature closure errors may occur in any case but are particularly common when patients seem to be having an exacerbation of a known disorder—eg, if a woman with a long history of migraine presents with a severe headache (and actually has a new subarachnoid hemorrhage), the headache may be mistakenly assumed to be another attack of migraine. A variation of premature closure occurs when subsequent clinicians (eg, consultants on a complicated case) unquestioningly accept a previous working diagnosis without independently collecting and reviewing relevant data.

Anchoring errors occur when clinicians steadfastly cling to an initial impression even as conflicting and contradictory data accumulate. For example, a working diagnosis of acute pancreatitis is quite reasonable in a 60-yr-old man who has epigastric pain and nausea, who is sitting forward clutching his abdomen, and who has a history of several bouts of alcoholic pancreatitis that he states have felt similar to what he is currently feeling. However, if the patient states that he has had no alcohol in many years and has normal blood levels of pancreatic enzymes, clinicians who simply dismiss or excuse (eg, the patient is lying, his pancreas is burned out, the laboratory made a mistake) these conflicting data are committing an anchoring error. Clinicians should regard conflicting data as evidence of the need to continue to seek the true diagnosis (acute MI) rather than as anomalies to be disregarded. There may be no supporting evidence (ie, for the misdiagnosis) in some cases in which anchoring errors are committed.

Confirmation bias occurs when clinicians selectively accept clinical data that support a desired hypothesis and ignore data that do not (cherry-picking). Confirmation bias often compounds an anchoring error when the clinician uses confirmatory data to support the anchored hypothesis even when clearly contradictory evidence is also available. For example, a clinician may steadfastly cling to patient history elements suggesting acute coronary syndrome (ACS) to confirm the original suspicion of ACS even when serial ECGs and cardiac enzymes are normal.

Attribution errors involve negative stereotypes that lead clinicians to ignore or minimize the possibility of serious disease. For example, clinicians might assume that an unconscious patient with an odor of alcohol is "just another drunk" and miss hypoglycemia or intracranial injury, or they might assume that a known drug abuser with back pain is simply seeking drugs and miss an epidural abscess caused by use of dirty needles. Psychiatric patients who develop a physical disorder are particularly likely to be subject to attribution errors because not only may they be subject to negative stereotyping but they often describe their symptoms in unclear, inconsistent, or confusing ways, leading unwary clinicians to assume their complaints are of mental origin.

Affective error involves avoiding unpleasant but necessary tests or examinations because of fondness or sympathy for the patient (eg, avoiding a pelvic examination on a modest patient or blood cultures on a seriously ill patient who has poor veins).

Minimizing cognitive errors: Some specific strategies can help minimize cognitive errors. Typically, after history and physical examination are done, clinicians often form a working diagnosis based on heuristics. At this point, it is relatively easy to insert a formal pause for reflection, asking several questions:

• If it is *not* the working diagnosis, what else could it be?

• What are the most dangerous things it could be?

• Is there any evidence that is at odds with the working diagnosis?

These questions can help expand the differential diagnosis to include things that may have been left out because of cognitive errors and thus trigger clinicians to obtain further necessary information.

Testing

Test results may help make a diagnosis in symptomatic patients (diagnostic testing) or identify occult disease in asymptomatic patients (screening). However, test results may interfere with clinical decision making if the test poorly discriminates between patients with and without disease, if the result is

inconsistent with the clinical picture, or if the test result is improperly integrated into the clinical context.

Laboratory tests are imperfect and may mistakenly identify some healthy people as diseased (a false-positive result) or may mistakenly identify some affected people as disease-free (a false-negative result). A test's ability to correctly include or exclude disease depends on how likely a person is to have a disease (prior probability) and on the test's intrinsic operating characteristics.

Although diagnostic testing is often a critical contributor to clinical decision making, testing can have undesired or unintended consequences. Testing must be done with deliberation and purpose and with the expectation that the test result will reduce ambiguity surrounding patient problems and contribute to their health. In addition to the risk of providing incorrect information (thereby delaying initiation of treatment or inducing unnecessary treatment), laboratory tests consume limited resources and may themselves have adverse effects (eg, pneumothorax caused by lung biopsy) or may prompt additional unnecessary testing.

Defining a Positive Test Result

Among the most common tests are those that provide results along a continuous, quantitative scale (eg, blood glucose, WBC count). Such tests may provide useful clinical information throughout their ranges, but clinicians often use them to diagnose a condition by requiring that the result be classified as positive or negative (ie, disease present or absent) based on comparison to some established criterion or cutoff point. Such cutoff points are usually selected based on statistical and conceptual analysis that attempts to balance the rate of false-positive results (prompting unnecessary, expensive, and possibly dangerous tests or treatments) and false-negative results (failing to diagnose a treatable disease). Identifying a cutoff point also depends on having a gold standard to identify the disease in question.

Typically, such quantitative test results (eg, WBC count in cases of suspected appendicitis) follow some type of distribution curve (not necessarily a normal curve, although commonly depicted as such). The distribution of test results for patients with disease is centered on a different point than that for patients without disease. Some patients with disease have a very high or very low result, but most have a result centered on a mean. Conversely, some disease-free patients have a very high or very low result, but most have a result centered on a different mean from that for patients with disease. For most tests, the distributions overlap such that many of the possible test results occur in patients with and without disease; such results are more clearly illustrated when the curves are depicted on the same graph (see Fig. 342-2). Some patients above and below the selected cutoff point will be incorrectly characterized. Adjusting a cutoff point to identify more patients with disease (increase test sensitivity) also increases the number of false positives (poor specificity), and moving the cutoff point the other way to avoid falsely diagnosing patients

[**Fig. 342-2.** Distributions of test results.]

as having disease increases the number of false negatives. Each cutoff point is associated with a specific probability of true-positive and false-positive results.

Receiver operating characteristic (ROC) curves: Graphing the fraction of true-positive results (number of true positives/number with disease) against the fraction of false-positive results (number of false positives/number without disease) for a series of cutoff points generates what is known as an ROC curve. The ROC curve graphically depicts the tradeoff between the sensitivity and specificity when the cut off point is adjusted (see Fig. 342-3).

[**Fig. 342-3.** Typical receiver operating characteristic (ROC) curve.]

By convention, the true-positive fraction is placed on the y-axis, and the false-positive fraction is placed on the x-axis. The greater the area under the ROC curve, the better the test discriminates between patients with or without disease.

ROC curves allow tests to be compared over a variety of cutoff points. In the example, Test A performs better than Test B over all ranges. ROC curves also assist in the selection of the cutoff point designed to

maximize a test's utility. If a test is designed to confirm a disease, a cutoff point with greater specificity and lower sensitivity is selected. If a test is designed to screen for occult disease, a cutoff point with greater sensitivity and lower specificity is selected.

Test Characteristics

Some clinical variables have only 2 possible results (eg, alive/dead, pregnant/not pregnant); such variables are termed categorical and dichotomous. Other categorical results may have many discrete values (eg, blood type, Glasgow Coma Scale) and are termed nominal or ordinal. Nominal variables such as blood type have no particular order. Ordinal variables such as the Glasgow Coma Scale have discrete values that are arranged in a particular order. Other clinical variables, including many typical diagnostic tests, are continuous and have an infinite number of possible results (eg, WBC count, blood glucose level). Many clinicians select a cutoff point that can cause a continuous variable to be treated as a dichotomous variable (eg, patients with a fasting blood glucose level > 126 mg/dL are considered to have diabetes). Other continuous diagnostic tests have diagnostic utility when they have multiple cutoff points or when ranges of results have different diagnostic value.

When test results can be defined as positive or negative, all possible outcomes can be recorded in a simple 2×2 table (see Table 342-2) from which important discriminatory test characteristics, including sensitivity, specificity, positive and negative predictive value, and likelihood ratio (LR), can be calculated (see Table 342-3).

Sensitivity, specificity, and predictive values: Sensitivity, specificity, and predictive values are typically considered characteristics of the test itself, independent of the patient population.

Sensitivity is the likelihood of a positive test result in patients with disease (true-positive rate); a test that is positive in 8 of 10 patients with a disease has a sensitivity of 0.8 (also expressed as 80%). Sensitivity represents how well a test detects the disease; a test with low sensitivity does not identify many patients with disease, and a test with high sensitivity is useful to exclude a diagnosis when results are negative. Sensitivity is the complement of the false-negative rate (ie, the false-negative rate plus the sensitivity = 100%).

[**Table 342-2.** Distribution of Hypothetical Test Results]

Specificity is the likelihood of a negative test result in patients without disease (true-negative rate); a test that is negative in 9 of 10 patients without disease has a specificity of 0.9 (or 90%). Specificity represents how well a test correctly identifies patients with disease because tests with high specificity have a low false-positive rate. A test with low specificity diagnoses many patients without disease as having disease. It is the complement of the false-positive rate.

Positive predictive value (PPV) is the proportion of patients with a positive test that actually have disease; if 9 of 10 positive test results are correct (true positive), the PPV is 90%. Because all positive test results have some number of true positives and some false positives, the PPV describes how likely it is that a positive test result in a given patient population represents a true positive.

Negative predictive value (NPV) is the proportion of patients with a negative test result that are actually disease free; if 8 of 10 negative test results are correct (true negative), the NPV is 80%. Because not all negative test results are true negatives, some patients with a negative test result actually have disease. The NPV describes how likely it is that a negative test result in a given patient population represents a true negative.

Likelihood ratios (LRs): Unlike sensitivity and specificity, which do not apply to specific patient probabilities, the LR allows clinicians to interpret test results in a specific patient provided there is a known (albeit often estimated) pre-test probability of disease.

The LR describes the change in pre-test probability of disease when the test result is known and answers the question, "How much has the post-test probability changed now that the test result is known?" Many

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[**Table 342-3.** Distribution of Test Results of a Hypothetical Leukocyte Esterase Test in a Cohort of 1000 Women with an Assumed 30% Prevalence of UTI]

tests are dichotomous; they are either above the cutoff point (positive) or below the cutoff point (negative) and there are only 2 possible results. Other tests give results that are continuous or occur over a range where multiple cutoff points are selected. The actual post-test probability depends on the magnitude of the LR (which depends on test operating characteristics) and the pre-test probability estimation of disease. When the test being done is dichotomous and the result is either positive or negative, the sensitivity and specificity can be used to calculate positive LR (LR+) or negative LR (LR-).

- **LR+:** The ratio of the likelihood of a positive test result occurring in patients with disease (true positive) to the likelihood of a positive test result in patients without disease (false positive)

- **LR-:** The ratio of the likelihood of a negative test result in patients with disease (false negative) to the likelihood of a negative test result in patients without disease (true negative)

When the result is continuous or has multiple cutoff points, the ROC curve, not sensitivity and specificity, is used to calculate an LR that is no longer described as LR+ or LR-.

Because the LR is a ratio of mutually exclusive events rather than a proportion of a total, it represents odds (see Sidebar 342-1) rather than probability. For a given test, the LR is different for positive and negative results.

For example, given a positive test result, an LR of 2.0 indicates the odds are 2:1 (true positives:false positives) that a positive test result represents a patient with disease. Of 3 positive tests, 2 would occur in patients with disease (true positive) and 1 would occur in a patient without disease (false positive). Because true positives and false positives are components of sensitivity and specificity calculations, the LR+ can also be calculated as sensitivity/(1 - specificity). The greater the LR+, the more information a positive test result provides; a positive result on a test with an LR+ > 10 is considered strong evidence in favor of a diagnosis. In other words, the pre-test probability estimation moves strongly toward 100% when a positive test has a high LR+.

For a negative test result, an LR- of 0.25 indicates that the odds are 1:4 (false negatives:true negatives) that a negative test result represents a patient with disease. Of 5 negative test results, 1 would occur in a patient with disease (false negative) and 4 would occur in patients without disease (true negative). The LR- can also be calculated as (1 - sensitivity)/specificity. The smaller the LR-, the more information a negative test result provides; a negative result on a test with an LR < 0.1 is considered strong evidence against a diagnosis. In other words, the pre-test probability estimation moves strongly toward 0% probability when a negative test has a low LR-.

Test results with LRs of 1.0 carry no information and do not affect the post-test probability of disease.

LRs are convenient for comparing tests and are also used in Bayesian analysis (see p. 3394) to interpret test results. Just as sensitivity and specificity change as cutoff points change, so do LRs. As a hypothetical example, a high cutoff for WBC count (eg, 20,000/µL) in a possible case of acute appendicitis is more specific and would have a high LR+ but also a high (and thus not very informative) LR-; choosing a much lower and very sensitive cutoff (eg, 10,000/µL) would have a low LR- but also a low LR+.

Dichotomous Tests

An ideal dichotomous test would have no false positives or false negatives; all patients with a positive test result would have disease (100% PPV), and all patients with a negative test result would not have disease (100% NPV).

In reality, all tests have false positives and false negatives, some tests more than others. To illustrate the

consequences of imperfect sensitivity and specificity on test results, consider hypothetical results (Table 342-3) of urine dipstick leukocyte esterase testing in a group of 1000 women, 300 (30%) of whom have a UTI (as determined by a gold-standard test such as urine culture). This scenario assumes for illustrative purposes that the dipstick test has sensitivity of 71% and specificity of 85%.

Sensitivity of 71% means that only 213 (71% of 300) women *with* UTI would have a positive test result. The remaining 87 would have a negative test result. Specificity of 85% means that 595 (85% of 700) women *without* UTI would have a negative test result. The remaining 105 would have a positive test result. Thus, of 318 positive test results, only 213 would be correct (213/318 = 67% PPV); a positive test result makes the diagnosis of UTI more likely than not but not certain. There would also be 682 negative tests, of which 595 are correct (595/682 = 87% NPV), making the diagnosis of UTI much less likely but still possible; 13% of patients with a negative test result would actually have a UTI.

However, the PPVs and NPVs derived in this patient cohort cannot be used to interpret results of the same test when the underlying incidence of disease (pre-test or prior probability) is different. Note the effects of changing disease incidence to 5% (see Table 342-4). Now most positive test results are false, and the PPV is only 20%; a patient with a positive test result is actually more likely to *not* have a UTI. However, the NPV is now very high (98%); a negative result essentially rules out UTI.

Note that in both patient cohorts, even though the PPV and NPV are very different, the LRs do not change because the LRs are determined only by test sensitivity and specificity.

Clearly, a test result does not provide a definitive diagnosis but only estimates the probability of a disease being present or absent, and this post-test probability (likelihood of disease given a specific test result) varies greatly based on the pre-test probability of disease as well as the test's sensitivity and specificity (and thus its LR).

Pre-test probability is not a precise measurement; it is based on clinical judgment of how strongly the symptoms and signs suggest the disease is present, what factors in the patient's history support the diagnosis, and how common the disease is in a representative population. Many clinical scoring systems are designed to estimate pre-test probability; adding points for various clinical features facilitates the calculation of a score. For example, there are criteria for predicting pre-test probability of pulmonary embolism (see p. 1910). Higher calculated scores yield higher estimated probabilities.

[**Table 342-4.** Distribution of Test Results of a Hypothetical Leukocyte Esterase Test in a Cohort of 1000 Women with an Assumed 5% Prevalence of UTI]

Continuous Tests

Many test results are continuous and may provide useful clinical information over a wide range of results. Clinicians often select a certain cutoff point to maximize the test's utility. For example, a WBC count > 15,000 may be characterized as positive; values < 15,000 as negative. When a test yields continuous results but a certain cutoff point is selected, the test operates like a dichotomous test. Multiple cutoff points can also be selected. Sensitivity, specificity, PPV, NPV, LR+, and LR- can be calculated for single or multiple cutoff points.
Table 342-5 illustrates the effect of changing the cutoff point of the WBC count in patients suspected of having appendicitis.

Alternatively, it can be useful to group continuous test results into levels. In this case, results are not characterized as positive or negative because there are multiple possible results, so although an LR can be determined for each level of results, there is no longer a distinct LR+ or LR-. For example, Table 342-6 illustrates the relationship between WBC count and bacteremia in febrile children. Because the LR is the probability of a given result in patients with disease divided by the probability of that result in patients without the disease, the LR for each grouping of WBC count is the probability of bacteremia in that group divided by the probability of no bacteremia.

Grouping continuous variables allows for much greater use of the test result than when a single cutoff

point is established. Using Bayesian analyses, the LRs in Table 342-6 can be used to calculate the post-test probability.

For continuous test results, if an ROC curve is known, calculations as shown in Table 342-6 do not have to be done; LRs can be found for various points over the range of results using the slope of the ROC curve at the desired point.

Bayes' Theorem

The process of using the pre-test probability of disease and the test characteristics to calculate the post-test probability is referred to as Bayes' theorem or Bayesian revision. For routine clinical use, Bayesian methodology typically takes several forms:

• Odds-likelihood formulation (calculation or nomogram)

• Tabular approach

Odds-likelihood calculation: If the pre-test probability of disease is expressed as its odds and because a test's LR represents odds, the product of the 2 represents the post-test odds of disease (analogous to multiplying 2 probabilities together to calculate the probability of simultaneous occurrence of 2 events):

Pre-test odds × LR = post-test odds

Because clinicians typically think in terms of probabilities rather than odds, probability can be converted to odds (and vice versa) with these formulas:

Odds = probability/1 - probability
Probability = odds/odds + 1

Consider the example of UTI as given in Table 342-3, in which the pre-test probability of UTI is 0.3, and the test being used has an LR+ of 4.73 and an LR- of 0.34. A pre-test probability of 0.3 corresponds to odds of 0.3/(1 - 0.3) = 0.43. Thus, the post-test odds that a

[**Table 342-5.** Effect of Changing the Cutoff Point of the WBC Count in Patients Suspected of Having Appendicitis]

[**Table 342-6.** Using WBC Count Groups to Determine Likelihood Ratio of Bacteremia in Febrile Children*]

UTI is present in a patient with a positive test result equals the product of the pre-test odds and the LR+; 4.73 × 0.43 = 2.03, which represents a post-test probability of 2.03/(1 + 2.03) = 0.67. Thus, Bayesian calculations show that a positive test result increases the pre-test probability from 30% to 67%, the same result obtained in the PPV calculation in Table 342-3.

A similar calculation is done for a negative test; post-test odds = 0.34 × 0.43 = 0.15, corresponding to a probability of 0.15/(1 + 0.15) = 0.13. Thus, a negative test result decreases the pre-test probability from 30% to 13%, again the same result obtained in the NPV calculation in Table 342-3.

Many medical calculator programs that run on handheld devices are available to calculate post-test probability from pre-test probability and LRs.

Odds-likelihood nomogram: Using a nomogram is particularly convenient because it avoids the need to convert between odds and probabilities or create 2×2 tables.

The Fagan nomogram is depicted in
Fig. 342-4. To use the nomogram, a line is drawn from the pre-test probability through the LR. The post-test probability is the point at which this line intersects the post-test probability line. Sample lines in the

figure are drawn using data from the UTI test in Table 342-3. Line A represents a positive test result; it is drawn from pre-test probability of 0.3 through the LR+ of 4.73 and gives a post-test value of slightly < 0.7, similar to the calculated probability of 0.67. Line B represents a negative test result; it is drawn from pre-test probability of 0.3 through the LR- value of 0.34 and gives a post-test value slightly > 0.1, similar to the calculated probability of 13%.

Although the nomogram appears less precise than calculations, typical values for pre-test probability are often estimates, so the apparent precision of calculations is usually misleading.

Tabular approach: Often, LRs of a test are not known, but sensitivity and specificity are known, and pre-test probability can be estimated. In this case, Bayesian methodology can be done using a 2×2 table illustrated in
Table 342-7 using the example from Table 342-3. Note that this method shows that a positive test result increases the probability of a UTI to 67%, and a negative result decreases it to 13%, the same results obtained by calculation using LRs.

Sequential Testing

Clinicians often do tests in sequence during many diagnostic evaluations. If the pre-test odds before sequential testing are known and the LR for each of the tests in sequence is known, post-test odds can be calculated using the following formula:

Pre-test odds × LR1 × LR2 × LR3 = post-test odds

This method is limited by the important assumption that each of the tests is conditionally independent of each other.

Screening Tests

Patients often must consider whether to be screened for occult disease. The premises of a

[**Fig. 342-4.** Fagan nomogram.]

screening program are that early detection improves outcome in patients with occult disease and that the false-positive results that often occur in screening do not create a burden (eg, costs and adverse effects of confirmatory testing, unwarranted treatment) that exceeds such benefit. To minimize these possible burdens, clinicians must choose the proper

[**Table 342-7.** Interpretation of a Hypothetical Leukocyte Esterase (LE) Test Result in a Cohort of 1000 Women Assuming a 30% Prevalence of UTI (Pre-Test Probability), Test Sensitivity 71%, and Specificity 85%*]

screening test. Screening is not appropriate when treatments are ineffective or the disease is very uncommon (unless a subpopulation can be identified in which prevalence is higher).

Theoretically, the best test for both screening and diagnosis is the one with the highest sensitivity *and* specificity. However, such highly accurate tests are often complex, expensive, and invasive (eg, coronary angiography) and are thus not practical for screening large numbers of asymptomatic people. Typically, some tradeoff in sensitivity, specificity, or both must be made when selecting a screening test.

Whether a clinician chooses a test that optimizes sensitivity or specificity depends on the consequences of a false-positive or false-negative test result as well as the pre-test probability of disease. An ideal screening test is one that is always positive in nearly every patient with disease so that a negative result confidently excludes disease in healthy patients. For example, in testing for a serious disease for which an effective treatment is available (eg, coronary artery disease), clinicians would be willing to tolerate more false positives than false negatives (lower specificity and high sensitivity). Although high sensitivity is a very important attribute for screening tests, specificity also is important in certain screening strategies. Among populations with a higher prevalence of disease, the PPV of a screening test

increases; as prevalence decreases, the post-test or posterior probability of a positive result decreases. Therefore, when screening for disease in high-risk populations, tests with a higher sensitivity are preferred over those with a higher specificity because they are better at ruling out disease (fewer false negatives). On the other hand, in low-risk populations or for uncommon diseases for which therapy has lower benefit or higher risk, tests with a higher specificity are preferred.

Multiple screening tests: With the expanding array of available screening tests, clinicians must consider the implications of a panel of such tests. For example, test panels containing 8, 12, or sometimes 20 blood tests are often done when a patient is admitted to the hospital or is first examined by a new clinician. Although this type of testing may be helpful in screening patients for certain diseases, using the large panel of tests has potentially negative consequences. By definition, a test with a specificity of 95% gives false-positive results in 5% of healthy, normal patients. If 2 different tests with such characteristics are done, each for a different occult disease, in a patient who actually does not have either disease, the chance that both tests will be negative is 95% × 95%, or about 90%; thus, there is a 10% chance of at least one false-positive result. For 3 such tests, the chance that all 3 would be negative is 95% × 95% × 95%, or 86%, corresponding to a 14% chance of at least one false-positive result. If 12 different tests for 12 different diseases are done, the chance of obtaining at least one false-positive result is 46%. This high probability underscores the need for caution when deciding to do a screening test panel and when interpreting its results.

Testing Thresholds

A laboratory test should be done only if its results will affect management; otherwise the expense and risk to the patient are for naught. Clinicians can sometimes make the determination of when to test by comparing pre-test and post-test probability estimations with certain thresholds. Above a certain probability threshold, benefits of treatment outweigh risks (including the risk of mistakenly treating a patient without disease), and treatment is indicated. This point is termed the treatment threshold (TT) and is determined as described previously (see p. 3386). By definition, testing is unnecessary when pre-test probability is already above the TT. But testing is indicated if pre-test probability is below the TT *as long as a positive test result could raise the post-test probability above the TT*. The lowest pre-test probability at which this can occur depends on test characteristics (eg, LR+) and is termed the testing threshold.

Conceptually, if the best test for a serious disorder has a low LR+, and the TT is high, it is understandable that a positive test result might not move the post-test probability above the TT in a patient with a low but worrisome pre-test probability (eg, perhaps 10% or 20%).

For a numerical illustration, consider the previously described case of a possible acute MI (see p. 3386) in which the balance between risk and benefit determined a TT of 25%. When the probability of MI exceeds 25%, thrombolytic therapy is given. When should a rapid echocardiogram be done before giving thrombolytic therapy? Assume a hypothetical sensitivity of 60% and a specificity of 70% for echocardiography in diagnosing an MI; these percentages correspond to an LR+ of 60/(100 - 70) = 2 and an LR- of (100 - 60)/70 = 0.57.

The issue can be addressed mathematically (pre-test odds × LR = post-test odds) or more intuitively graphically by using the Fagan nomogram (see Fig. 342-5). On the nomogram, a line connecting the TT (25%) on the post-test probability line through the LR+ (2.0) on the middle LR line intersects a pre-test probability of about 0.14. Clearly, a positive test in a patient with any pre-test probability < 14% would still result in a post-test probability less than the TT. In this case, echocardiography would be useless because even a positive result would not lead to a decision to treat; thus, 14% pre-test probability is the testing threshold *for this particular test* (see Fig. 342-6). Another test with a different LR+ would have a different testing threshold.

Because 14% still represents a significant risk of MI, it is clear that a disease probability below the testing threshold (eg, a 10% pre-test probability) does not necessarily mean disease is ruled out, just that a positive test result on the particular test in question would not change management and thus *that* test is not indicated. In this situation, the clinician would observe the patient for further findings that might elevate the pre-test probability above the testing threshold. In practice, because multiple tests are often

available for a given disease, sequential testing (see p. 3395) might be used.

This example considers a test that of itself poses no risk to the patient. If a test has serious risks (eg, cardiac catheterization), the testing threshold should be higher; quantitative calculations can be done but are complex. Thus, decreasing a test's sensitivity and specificity or increasing its risk narrows the range of probabilities of disease over which testing is the best strategy. Improving the test's ability to discriminate or decreasing its risk broadens the range of probabilities over which testing is the best strategy.

A possible exception to the proscription against testing when pre-test probability is below the testing threshold (but is still worrisome) might be if a negative test result could *reduce* post-test probability below the point at which disease could be considered ruled out. This determination requires a subjective judgment of the degree of certainty required to say a disease is ruled out and, because low probabilities are involved, particular attention to any risks of testing.

Economic Analyses

Given limited societal and personal resources and restrictions under health insurance, cost considerations have become more relevant in clinical decision making. Limited resources should not be wasted; their allocation depends on an understanding of the various costs and outcomes resulting from strategies of care.

Cost

The elements included in cost analysis are determined by the perspective of the analysis. Different perspectives often result in different conclusions based on which costs and outcomes are considered.

- **Providers** (eg, health care practitioners, institutions) typically consider only costs within the organization (eg, personnel, supplies, overhead).

- **Payors** (eg, insurance companies) consider only the reimbursements they have to make.

- **Patients** consider out-of-pocket expenses (eg, cost of insurance, deductibles, transportation, parking) and lost income (for themselves and their family).

[**Fig. 342-5.** Fagan nomogram used to determine need to test.]

[**Fig. 342-6.** Depiction of testing and treatment thresholds.]

From a societal perspective, all such costs are taken into account along with the costs of lost productivity and costs of treating other diseases (iatrogenic and naturally occurring) that may develop in patients who recover from the disease being treated. For example, a young man cured of lymphoma may develop leukemia or coronary artery disease years later. Cost analysis of a screening program needs to include the costs of pursuing false-positive results, which in a screening test for a disease with a low prevalence often exceed the costs of evaluating and treating patients who actually have the disease.

Marginal cost: The marginal cost is the cost of providing (or withholding) an additional unit of service. This cost is often one of the most relevant for an individual clinician's medical decision making and is typically quite different from the overall cost allocated to that service. For example, a hospital may have determined that $50 is the cost of providing a chest x-ray. However, a clinical protocol to better identify patients requiring x-rays that resulted in one fewer chest x-ray a day (with no change in outcome) would not "save" the hospital $50 because personnel and overhead expenses would be unchanged; only the expense of x-ray film would be eliminated. Hence the marginal cost to the hospital of one chest x-ray is essentially the cost of one piece of x-ray film (even less if digital capture techniques are used). Note that marginal cost varies with volume in a quantum fashion; adding or withholding a larger number of x-rays would at some point dictate a change in personnel and perhaps x-ray equipment, resulting in a different marginal cost. Additionally, the marginal cost is different for the payors; withholding one chest x-ray would save the payors the entire amount they typically reimburse for that x-ray, a figure far higher than the

hospital's marginal cost.

Outcome

The effectiveness of medical care is measured by change in outcome. Outcomes can be

• Patient oriented

• Process oriented

• Disease oriented

Patient-oriented outcomes can be reduced to one of the three Ds:

• Death

• Disability

• Discomfort

Patient-oriented outcomes are arguably the most important. Improvements in process (eg, reducing the time to antibiotic administration or to operating room) or disease manifestations (eg, shrinking tumor size, improving O_2 saturation) that do *not* reduce mortality, disability, or discomfort at all can hardly be said to benefit the patient. For example, lidocaine was once routinely given to patients with MI because it was known to reduce the incidence of ventricular fibrillation (improved disease outcome). Lidocaine treatment continued for many years before studies showed it did not decrease mortality (no change in patient outcome), and so the practice was stopped.

Change in raw mortality is the most common way to evaluate effect on death. In more complex analysis, death and disability are often evaluated in combination as the quality-adjusted life year (QALY); treatment that results in an additional year of life at 100% of normal functioning is credited with 1 QALY; treatment that results in an additional year of life at only 75% functioning is credited with 0.75 QALY. QALY is more difficult to apply to discomfort, but some believe it can be estimated by the time tradeoff method: A person estimates how many years of discomfort would be acceptable vs a shorter period of perfect health. For example, if a person would prefer 9 yr of health to 10 yr of chronic pain (but would prefer the 10 yr of pain to only 8 yr of life), then each year of life with pain is credited with 9/10 = 0.9 QALY. All such QALY estimates are somewhat problematic because people vary widely in risk tolerance and acceptance for various outcomes.

The **number needed to treat** (NNT) or harm is another way to quantify patient outcome; NNT is the reciprocal of the absolute change in a dichotomous outcome (death, disability). Thus, if a drug causes a 3% net decrease in mortality, 1/0.03 = 33.3 patients need to be treated to prevent 1 death. Similarly, for a drug that causes leukopenia in 8% of patients, 1/0.08 or 12.5 need to be treated to harm 1 person.

Cost-Benefit Analysis

Simple analysis of the economic consequences of outcomes (cost-benefit analysis) depends on assumptions about the perceived dollar value of prolonged life and improved health. Such assumptions are often arguable and rarely straightforward. Furthermore, although such analyses determine whether a given strategy saves costs or requires the net expenditure of resources, they do not indicate whether the expenditures are worthwhile.

Cost-effectiveness analysis tracks medical costs and health outcomes separately. Both outcome measures can be strongly affected by the perspective and duration of the analysis and by the underlying assumptions. Comparison of the costs and health outcomes of 2 management strategies results in 1 of 9 pairings (see
Table 342-8). When health outcomes are equivalent (center column), the choice should be based on cost; when costs are equivalent (center row), the choice should be based on outcome. When one strategy has

better outcomes *and* lower costs (upper right and lower left cells), the choice is clear. The decision is difficult only when the strategy that is more expensive also produces better outcomes (upper left and lower right cells); in such cases, the marginal cost-effectiveness ratio should be determined.

Marginal cost-effectiveness ratio: The marginal cost-effectiveness ratio is the additional cost of a strategy divided by the additional health outcome it achieves and thus pertains to the situation in which there is a choice between ≥ 2 effective management strategies. Greater health improvement for a given resource expenditure is derived when the ratio is lower.

For policy analysis, the most common measure of effectiveness is the QALY, making the units of the corresponding marginal cost-effectiveness ratio "additional dollars spent per QALY gained." However, the marginal cost-effectiveness ratio has been criticized because elderly patients or patients with life-limiting comorbidities have a smaller potential gain in survival from a treatment and therefore have a higher (less advantageous) cost-effectiveness ratio.

For example (see Table 342-9), consider no antiarrhythmic therapy vs prophylactic use of an implantable cardioverter-defibrillator (ICD) for patients who have survived several months after an acute anterior MI and who have a mildly depressed ejection fraction (between 0.3 and 0.4). (All figures and costs in this example are hypothetical.) Both strategies assume similar baseline costs for routine care ($78,300), but the ICD has an additional (marginal) cost of $53,100, based on the cost of the device and professional fees, initial hospitalization, and ongoing therapy (including extra physician visits, laboratory tests, drugs, rehospitalizations for ICD-related complications, and replacement of ICD generator or leads). If patients with an ICD have a slightly increased life expectancy (7.87 vs 7.42 QALY), the marginal effectiveness of ICD therapy is 7.87 - 7.42 = 0.45 QALY. Thus, prophylactic ICD enhances survival compared to no antiarrhythmic therapy at a cost of $53,100/0.45 QALY, or $118,000/QALY.

Now assume that a third strategy, prophylactic amiodarone therapy, is available. This therapy is less expensive but also less effective than ICD. The effect of adding this third intermediate strategy is noteworthy because marginal cost-effectiveness ratios are calculated sequentially when there are multiple strategies (Table 342-9, Analysis 2). The marginal cost-effectiveness ratio of amiodarone is lower

[**Table 342-8.** Cost-Effectiveness Comparison of Management Strategies A and B]

[**Table 342-9.** Calculating a Marginal Cost-Effectiveness Ratio]

($68,519/QALY gained) than that for an ICD calculated in the previous example, and furthermore, because the effectiveness of an ICD is now compared to amiodarone rather than to no therapy, the addition of this intermediate cost strategy with partial effectiveness increases the ICD's marginal cost-effectiveness ratio from $118,000 to $192,222/QALY gained. This analysis suggests that for an expensive therapy such as an ICD, an attempt should be made to identify subpopulations expected to reap the greatest benefit.

Chapter 343. Principles of Radiologic Imaging

Introduction

Continuing improvements in radiologic imaging make it increasingly useful in diagnostic evaluation. Primary care and referring physicians work with radiologists who specialize in diagnostic imaging to choose the best imaging test for each evaluation. Many imaging tests use ionizing radiation (x-rays and radionuclides) and radiographic contrast agents; the associated risks to patients are usually small but should be considered.

Risks of Ionizing Radiation

Most diagnostic tests that use ionizing radiation (eg, x-rays, CT, radionuclide scanning) expose patients to relatively low doses of radiation that are generally considered safe. However, all ionizing radiation is harmful, and there is no threshold below which no harmful effect occurs, so every effort is made to minimize radiation exposure. Doses vary by type of imaging test (see Table 343-1).

There are various ways to measure radiation exposure:

- The **absorbed dose** is the amount of radiation absorbed per unit mass. It is expressed in special units of gray (Gy) and mGy. It was previously expressed as rad (1 mGy = 0.1 rad).

- The **equivalent dose** is the absorbed dose multiplied by a radiation weighting factor that adjusts for tissue effects based on the type of radiation delivered (eg, x-rays, gamma rays, electrons). It is expressed in sieverts (Sv) and mSv. It was previously expressed in rem (1 mSv = 0.1 rem). For x-rays, including CT, the radiation weighting factor is 1.

- The **effective dose** is a measure of cancer risk; it adjusts the equivalent dose based on the susceptibility of the tissue exposed to radiation (eg, gonads are most susceptible). It is expressed in Sv and mSv. In the US, the average yearly effective dose of environmental

[**Table 343-1.** Typical Radiation Doses*]

background radiation (from cosmic radiation and natural isotopes) is 3 mSv. The effective dose is higher in young people.

Radiation may be harmful if the total accumulated dose for a person is high, as when multiple scans are done, because most scans require a high dose. Radiation dose is also a concern in certain high-risk situations (eg, during early pregnancy, infancy, or early childhood; in young women who require mammography).

In the US, CT accounts for > 15% of all imaging tests but for about 70% of total radiation delivered during diagnostic imaging. Multidetector CT scanners, which are usually used now, deliver about 40 to 70% more radiation per scan than do older single detector CT scanners.

Estimated risk of cancer due to radiation exposure in diagnostic imaging has been extrapolated from studies of people exposed to very high radiation doses (eg, survivors of the atomic bomb explosions at Hiroshima and Nagasaki). This analysis suggests a small but real risk of cancer if radiation doses are in the tens of mGy (as used in CT). A CT pulmonary angiogram, routinely done to detect pulmonary embolism, delivers about as much radiation to the breasts as about 10 to 25 two-view mammograms.

Risk is higher in young patients because they live longer, giving cancers more time to develop, and because more cellular growth (and thus susceptibility to DNA damage) occurs in the young. For a 1-yr-old who has a CT scan of the abdomen, estimated lifetime risk of developing cancer is increased by 0.18%. If an elderly patient has this test, risk is lower.

Risk also depends on the tissue being irradiated; for example, risk is higher for breast and abdominal

tissue than for brain tissue.

Radiation during pregnancy: Risks of radiation depend on dose, type of test, and area being examined. The fetus may be exposed to much less radiation than the mother; exposure to the fetus is negligible during head, cervical spine, and extremity x-rays and during mammography when the uterus is shielded. The extent of uterine exposure depends on gestational age and thus uterine size. The effects of radiation depend on the age of the conceptus (the time from conception).

Recommendations: Diagnostic imaging using ionizing radiation, especially CT, should be done only when clearly required. Alternatives should be considered. For example, in young children, minor head injury can often be diagnosed and treated based on clinical findings, and appendicitis can often be diagnosed by ultrasonography. However, necessary tests should not be withheld, even if risk is high, as long as the benefit outweighs the potential risk.

Before diagnostic tests are done in women of child-bearing age, pregnancy should be considered, particularly because risks of radiation exposure are highest during early, often unrecognized pregnancy. The uterus should be shielded in such women when possible.

Radiographic Contrast Agents and Contrast Reactions

Radiopaque contrast agents are often used in radiography and fluoroscopy to help delineate borders between tissues with similar radiodensity. Most contrast agents are iodine-based. Iodinated contrast agents may be ionic or nonionic. Ionic contrast agents, which are salts, are hyperosmolar to blood. These agents should not be used for myelography or in injections that may enter the spinal canal (because neurotoxicity is a risk) or the bronchial tree (because pulmonary edema is a risk). Nonionic contrast agents may be low-osmolar (which is still hyperosmolar relative to blood) or iso-osmolar (with the same osmolarity as blood). Newer nonionic contrast agents are now routinely used at many institutions because they have fewer adverse effects.

The most serious contrast reactions are allergic-type reactions and contrast nephropathy (renal damage after intravascular injection of a contrast agent).

Allergic-type contrast reactions: Reactions vary in severity:

- Mild (eg, cough, itching, nasal congestion)
- Moderate (eg, dyspnea, wheezing, slight changes in pulse or BP)
- Severe (eg, respiratory distress, arrhythmias such as bradycardia, seizures, shock, cardiopulmonary arrest)

The mechanism is anaphylactoid (see p. 1120); risk factors include a previous reaction to injected contrast agents, asthma, and allergies.

Treatment begins by stopping contrast infusion. For mild or moderate reactions, diphenhydramine 25 to 50 mg IV is usually effective. Treatment of severe reactions depends on the type of reaction and may include oxygen, epinephrine, IV fluids, and possibly atropine (for bradycardia).

In patients at high risk of contrast reactions, imaging tests that do not require iodinated contrast should be used. If contrast is necessary, a nonionic agent should be used, and patients should be premedicated with prednisone (50 mg po 13 h, 7 h, and 1 h before injection of contrast) and diphenhydramine (50 mg po or IM 1 h before the injection). If patients require imaging immediately, they can be given diphenhydramine 50 mg po or IM 1 h before injection of contrast and hydrocortisone 200 mg IV q 4 h until imaging is completed.

Contrast nephropathy: In some patients, intravascular injection of an iodinated contrast agent causes serum creatinine to increase transiently. Most of these patients have no symptoms, and nearly all recover normal function within 1 wk. However, < 1% of patients require dialysis or develop chronic kidney

disease, indicating contrast nephropathy. Common risk factors include the following:

- Preexisting renal insufficiency (elevated creatinine)
- Diabetes mellitus
- Hypertension
- Heart failure
- Multiple myeloma
- Age > 70
- Use of other nephrotoxic drugs
- Solitary kidney (with elevated creatinine)

In patients at risk of developing acute renal failure after receiving iodinated intravascular contrast, reduced dose of contrast, use of iso-osmolality agent, and hydration should be considered. Many hydration regimens exist; one example is IV administration of 0.9% normal saline at 1 mL/kg for 24 h beginning a few hours before the procedure. Acetylcysteine may be given as premedication for patients at risk of developing nephrotoxicity, but its efficacy is uncertain. Oral antihyperglycemic drugs, such as metformin, should be withheld for 48 h after IV contrast administration to avoid drug accumulation if contrast-induced nephrotoxicity occurs. Because many protocols dealing with contrast agents and reactions are specific and continually updated, it is important to discuss such details with the imaging department.

Angiography

Angiography is sometimes called conventional angiography to distinguish it from CT angiography (CTA) and magnetic resonance angiography (MRA). Angiography provides detailed images of blood vessels, commonly those in the heart, lungs, brain, and legs. Angiography can provide still images or motion pictures (called cineangiography).

IV contrast is injected through a catheter inserted into a blood vessel that connects with the vessel to be imaged. A local anesthetic or a sedative may be used. If the catheter is inserted into an artery, the insertion site must be steadily compressed for 10 to 20 min after all instruments are removed. Patients may need to lie flat for several hours or be hospitalized to reduce risk of bleeding at the puncture site. Angiography, although invasive, is relatively safe.

Uses

Angiography is the traditional gold standard for evaluating vascular lesions (eg, stenosis, obstruction, arteriovenous or other vascular malformations, aneurysms, dissections, sometimes vasculitis).

- **Coronary angiography** is usually done before percutaneous or surgical interventions involving the coronary arteries or heart valves. It is usually done with cardiac catheterization (see p. 2048).
- **Pulmonary angiography** is the gold standard for diagnosis of pulmonary embolism.
- **Cerebral angiography** may be indicated after stroke or transient ischemic attack (TIA)—eg, if stenting or carotid endarterectomy is being considered.
- **Iliac and femoral angiography** may be indicated before interventions to treat peripheral arterial disease.
- **Aortography** is sometimes done to diagnose and provide anatomic detail about aortic aneurysms,

aortic dissection, and aortic regurgitation.

• **Angiography of the eye arteries** can be done using fluorescein dye.

Angioplasty, stenting, and sometimes vascular repair can be done during angiography.

Variations

Digital subtraction angiography: Images of arteries are taken before and after contrast injection; then a computer subtracts one image from the other. Images of structures other than arteries are thus eliminated, enabling the arteries to be seen more clearly.

Disadvantages

Contrast reactions occasionally occur (see p. 3403).

The injection site may become infected or bleed, sometimes forming a painful hematoma. Rarely, an artery is injured by the catheter. Very rarely, shock, seizures, renal failure, and cardiac arrest occur. Risk of complications is higher in the elderly, although it is still low. The radiation dose used in angiography can vary and be significant (eg, coronary angiography is associated with an effective radiation dose of 4.6 to 15.8 mSv). Angiography must be done by highly skilled physicians, usually interventional radiologists.

Computed Tomography

In CT, an x-ray source and x-ray detector housed in a doughnut-shaped assembly move circularly around a patient who lies on a motorized table that is moved through the machine. Usually, multidetector scanners with 4 to 64 or more rows of detectors are used because more detectors allow quicker scanning and higher-resolution images.

Data from the detectors essentially represent a series of x-ray images taken from multiple angles all around the patient. However, the images are not viewed directly but are sent to a computer, which quickly reconstructs them into 2-dimensional images (tomograms) representing a slice of the body in any plane desired. Data can also be used to construct detailed 3-dimensional images. For some CT scans, the table moves incrementally and stops when each scan (slice) is taken. For other CT scans, the table moves continuously during scanning; because the patient is moving in a straight line and the detectors are moving in a circle, the series of images appear to be taken in a spiral fashion around the patient—hence the term helical (spiral) CT.

These same principles of tomographic imaging can also be applied to radionuclide scanning, in which the sensors for emitted radiation encircle the patient and computer techniques convert the sensor data into tomographic images; examples include single-photon emission CT (SPECT) and positron-emission tomography (PET).

Uses

Compared with plain x-rays, the tomo-graphic slices of CT provide more spatial detail and can better differentiate between various soft-tissue densities. Because it provides so much more information, CT is preferred to plain x-rays for imaging most intracranial, head and neck, spinal, intrathoracic, and intra-abdominal structures. Three-dimensional images of lesions can help surgeons plan surgery. CT is the most accurate study for detecting and localizing urinary calculi.

CT may be done with or without IV contrast. Noncontrast CT is used to detect acute hemorrhage in the brain, urinary calculi, and lung nodules, as well as to characterize bone fractures and other skeletal abnormalities. IV contrast is used to improve imaging of tumors, infection, inflammation, and trauma in soft tissues and to assess the vascular system, as when pulmonary embolism, aortic aneurysm, or aortic dissection is suspected.

Oral or occasionally rectal contrast is used for abdominal imaging; sometimes gas is used to distend the lower GI tract and make it visible. Contrast in the GI tract helps distinguish the GI tract from surrounding structures. Standard oral contrast is barium-based, but low-osmolar iodinated contrast should be used when intestinal perforation is suspected or when risk of aspiration is high.

Variations

Virtual colonoscopy: After gas is introduced into the rectum via a flexible, thin-diameter rubber catheter, CT of the entire colon is done. Virtual colonoscopy produces high-resolution 3-dimensional images of the colon that somewhat simulate the appearance of optical colonoscopy. This technique can show colon polyps and colon mucosal lesions as small as 5 mm. It is an alternative to conventional colonoscopy.

CT IV pyelography (CT IVP) or urography: IV contrast is injected. The procedure produces detailed images of the kidneys, ureters, and bladder. It is an alternative to conventional IV urography.

CT angiography: After a rapid bolus injection of IV contrast, thin-slice images are rapidly taken as the contrast opacifies arteries and veins. Advanced computer graphics techniques are used to remove images of surrounding soft tissues and to provide highly detailed images of blood vessels similar to those of conventional angiography. CT angiography is a less invasive alternative to conventional angiography.

Disadvantages

CT accounts for most diagnostic radiation exposure to patients collectively. If multiple scans are done, the total radiation dose may be high, placing the patient at potential risk (see p. 3402). Patients who have recurrent urinary tract stones or who have had major trauma are most likely to have multiple CT scans. The risk of radiation exposure vs benefit of the examination must always be considered because the effective radiation dose of one abdomen CT is equal to 500 chest x-rays.

Some CT scans use IV contrast, which has certain risks (see p. 3403). If barium extrava-sates outside the GI tract lumen, it can induce severe inflammation; if aspirated, barium can induce severe pneumonia. Barium can also become hard and inspissated, potentially precipitating intestinal obstruction. Gastrografin is safer, but the contrast and images of the GI tract it provides are not as good.

The CT table may not be able to accommodate very obese patients.

Magnetic Resonance Imaging

MRI uses magnetic fields and radio waves to produce images of thin slices of tissues (tomographic images). Normally, protons within tissues spin to produce tiny magnetic fields that are randomly aligned. When surrounded by the strong magnetic field of an MRI device, the magnetic axes align along that field. A radiofrequency pulse is then applied, causing the axes of all protons to momentarily align against the field in a high-energy state. After the pulse, some protons relax and resume their baseline alignment within the magnetic field of the MRI device. The magnitude and rate of energy release that occurs as the protons resume this alignment (T1 relaxation) and as they wobble (precess) during the process (T2 relaxation) are recorded as spatially localized signal intensities by a coil (antenna). Computer algorithms analyze these signals and produce anatomic images.

The relative signal intensity (brightness) of tissues in an MRI image is determined by factors such as the radiofrequency pulse and gradient waveforms used to obtain the image, intrinsic T1 and T2 tissue characteristics, and tissue proton density.

By controlling the radiofrequency pulse and gradient waveforms, computer programs produce specific pulse sequences that determine how an image is obtained (weighted) and how various tissues appear. Images can be T1-weighted, T2-weighted, or proton density-weighted. For example, fat appears bright (high signal intensity) on T1-weighted images and relatively dark (low signal intensity) on T2-weighted images; water and fluids appear relatively dark on T1-weighted images and bright on T2-weighted images. T1-weighted images optimally show normal soft-tissue anatomy and fat (eg, to confirm a fat-containing mass). T2-weighted images optimally show fluid and abnormalities (eg, tumors, inflammation,

trauma). In practice, T1- and T2-weighted images provide complementary information, so both are important for characterizing abnormalities.

Uses

MRI is preferred to CT when soft-tissue contrast resolution must be highly detailed (eg, to evaluate intracranial or spinal cord abnormalities, inflammation, trauma, suspected musculoskeletal tumors, internal joint derangement). MRI is also useful for evaluating the following:

- **Vascular imaging:** Magnetic resonance angiography (MRA) is used to image arteries with good diagnostic accuracy and is less invasive than conventional angiography. Gadolinium contrast is sometimes used. MRA can be used to image the thoracic and abdominal aorta and arteries of the brain, neck, kidneys, and lower extremities. Venous imaging (magnetic resonance venography) can also be done.

- **Hepatic and biliary tract abnormalities:** Magnetic resonance cholangiopancreatography (MRCP) is particularly valuable as a noninvasive, highly accurate method of imaging the biliary and pancreatic duct systems.

- **Masses in the female reproductive organs:** MRI is used to characterize adnexal masses and to stage uterine tumors.

- **Certain fractures:** For example, MRI can provide accurate images of hip fractures in patients with osteopenia.

- **Lytic bone metastases**

MRI can also be substituted for CT with contrast in patients with a high risk of contrast reactions.

Contrast: With MRI, contrast agents may be used to highlight vascular structures (for MRA) and to help characterize inflammation and tumors. The most commonly used agents are gadolinium derivatives, which have magnetic properties that affect proton relaxation times. MRI of intra-articular structures may include injection of a gadolinium derivative into a joint.

Variations

Diffusion (diffusion-weighted) MRI: Signal intensities are related to diffusion of water molecules in tissue. This type of MRI can be used to detect early cerebral ischemia and infarction and to differentiate intracranial cysts from solid masses.

Echo planar imaging: This ultrafast technique (images obtained in > 1 sec) is used for diffusion, perfusion, and functional imaging of the brain and heart. Its potential advantages include showing brain and heart activity and reducing motion artifacts. However, its use is limited because it requires special technical hardware and it is susceptible to other artifacts.

Functional MRI: Functional MRI is used to assess brain activity by location. In the most common type, the brain is scanned at low resolution very frequently (eg, every 2 to 3 sec). The change in oxygenated Hb can be discerned and used to estimate metabolic activity. Mechanisms of various neural mechanisms can be studied in research settings.

Gradient echo imaging: Gradient echo is a pulse sequence that can be used for fast imaging of moving blood and CSF (eg, in MRA). Because this technique is fast, it can reduce motion artifacts (eg, blurring) during imaging that requires patients to hold their breath (eg, during imaging of cardiac and abdominal structures).

Magnetic resonance spectroscopy (MRS): MRS combines the information obtained by MRI (mainly based on water and fat content of tissues) with that of nuclear magnetic resonance, or NMR; NMR provides information about tissue metabolites. Such information can help differentiate certain

abnormalities (eg, certain types of tumors).

Perfusion MRI: Perfusion MRI is a method of assessing relative cerebral blood flow. It can be used to detect an area of ischemia during imaging for stroke.

Disadvantages

MRI is relatively expensive and may not be available or available immediately.

Magnetic field: MRI is relatively contraindicated in patients with implanted materials that can be affected by powerful magnetic fields. These materials include ferromagnetic metal (containing iron), magnetically activated or electronically controlled medical devices (eg, pacemakers, implantable cardioverter defibrillators, cochlear implants), and nonferromagnetic metal electronically conductive wires or materials (eg, pacemaker wires, certain pulmonary artery catheters). Ferromagnetic material may be moved by the strong magnetic field and injure a nearby organ; movement is more likely if the material has been in place < 6 wk (before scar tissue forms). Ferromagnetic material can also cause imaging artifacts. Magnetically activated medical devices may malfunction when exposed to magnetic fields. Magnetic fields may induce current in conductive materials; this current may produce enough heat to burn tissues. Whether a specific device is compatible with MRI depends on the type of device, its components, and its manufacturer (see the MRI safety web site). Also, MRI machines with different magnetic field strengths have different effects on materials, so safety in one machine does not ensure safety in another.

The MRI magnetic field is very strong and always on. Thus, a ferromagnetic object (eg, an O_2 tank, a metal pole) at the entrance of the scanning room may be pulled into the magnet bore at high velocity and injure anyone in its path. The only way to separate the object from the magnet may be to turn off the magnetic field.

Claustrophobia: The imaging tube of an MRI machine is a tight, enclosed space that can trigger claustrophobia even in patients without preexisting phobias or anxiety. Also, some obese patients do not fit on the table or within the machine. Premedication with an anxiolytic (eg, alprazolam or lorazepam 1 to 2 mg po) 15 to 30 min before scanning is effective for most anxious patients. MRI scanners with an open side can be used. Its images may be inferior to those of enclosed scanners depending on the field strength of the magnet, but they are usually sufficient for making a diagnosis. Patients should be warned that the MRI machine makes loud, banging noises.

Contrast reactions: Gadolinium derivatives, if used, can cause headache, nausea, and pain, as well as sensation of cold at the injection site. However, serious contrast reactions are rare and much less common than with iodinated contrast agents. However, in patients with impaired renal function, nephrogenic systemic fibrosis is a risk. Nephrogenic systemic fibrosis is a rare but life-threatening disorder that involves the skin and probably internal organs, resulting in severe disability or death. For patients with impaired renal function, the following is recommended:

- Gadolinium should be used only when necessary.
- Before this agent is used, renal function should be checked (eg, based on patient history or laboratory tests such as GFR).
- The dose should be as small as possible, and the number of tests done should be limited if possible. If a second test is required, it should be delayed about 1 wk.

Radiography

Radiography involves the use of x-rays; the term "plain x-rays" is sometimes used to distinguish x-rays used alone from x-rays combined with other techniques (eg, CT). For plain x-rays, an x-ray beam is generated and passed through a patient to a piece of film or a radiation detector, producing an image. Different soft tissues attenuate x-ray photons differently, depending on tissue density; the denser the tissue, the whiter (more radiopaque) the image. The range of densities, from most to least dense, is represented by metal (white, or radiopaque), bone cortex (less white), muscle and fluid (gray), fat (darker

gray), and air or gas (black, or radiolucent).

Radiography is usually the most readily available imaging method. Typically, it is the first imaging method indicated to evaluate the extremities, chest, and sometimes the spine and abdomen. These areas contain important structures with densities that may differ from those of adjacent tissues. For example, radiography is a first-line test for detecting the following:

- **Fractures:** White bone is well seen because it is adjacent to gray soft tissues.
- **Pneumonia:** Inflammatory exudate that fills the lungs is well seen because it contrasts with adjacent air spaces.
- **Intestinal obstruction:** Dilated, air-filled loops of intestine are well seen amidst the surrounding soft tissue.

Variations

Contrast studies: When the density of adjacent tissues is similar, a radiopaque contrast agent (see p. 3403) is often added to one tissue or structure to differentiate it from its surroundings. Structures typically requiring a contrast agent include blood vessels (for angiography) and the lumina of the GI, biliary, and GU tracts. Gas may be used to distend the lower GI tract and make it visible. Other imaging tests (eg, CT, MRI) have largely replaced contrast studies because their tomographic images provide better anatomic localization of an abnormality.

Fluoroscopy: A continuous x-ray beam is used to produce images of moving structures or objects. Fluoroscopy is most often used with contrast agents (eg, in swallowing studies or coronary artery catheterization) or during medical procedures to guide placement of a lead, catheter, or needle (eg, in electro-physiologic testing or percutaneous coronary interventions).

Disadvantages

Diagnostic accuracy is limited in many situations. Other imaging tests may provide better image detail, be safer or faster, or have other advantages.

Contrast agents such as barium and gastrografin, if used, have disadvantages (see p. 3406), and IV contrast agents have risks (see p. 3403). Fluoroscopy may involve high doses of radiation.

Radionuclide Scanning

Radionuclide scanning uses the radiation released by radionuclides (called nuclear decay) to produce images. A radionuclide is an unstable isotope that becomes more stable by releasing energy as radiation. This radiation can include gamma-ray photons or particulate emission (such as positrons, used in PET). Radiation produced by radionuclides may be used for imaging or for treatment of certain disorders (eg, thyroid disorders).

A radionuclide, usually technetium-99m, is combined with different stable, metabolically active compounds to form a radiopharmaceutical that localizes to a particular anatomic or diseased structure (target tissue). The radiopharmaceutical is given by mouth or by injection. After the radionuclide has had time to reach the target tissue, images are taken with a gamma camera. Gamma rays emitted by the radionuclide interact with scintillation crystals in the camera, creating light photons that are converted into electrical signals by photomultiplier tubes. A computer summarizes and analyzes the signals and integrates them into 2-dimensional images. However, only signals near the camera's face can be accurately analyzed; thus, imaging is limited by the range of the camera.

Portable gamma cameras can provide radionuclide imaging at bedside. Generally, radionuclide scanning is considered safe (see Table 343-1).

Uses

The compound labeled with the radionuclide depends on the target tissue or indication:

- For imaging the skeleton, technetium-99m is combined with diphosphonate and used to check for bone metastasis or infection.
- For identifying inflammation, WBCs are labeled and used to identify inflammation.
- For localizing GI bleeding, RBCs are labeled.
- For imaging the liver, spleen, or bone marrow, sulfur colloid is labeled.
- For imaging the biliary tract, iminodiacetic acid derivatives are labeled and used to check for biliary obstruction, bile leaks, and gallbladder disorders.

Radionuclide scanning is also used to image the thyroid gland and the cerebrovascular, cardiovascular, respiratory, and GU systems. For example, in myocardial perfusion imaging, heart tissue takes up radionuclides (eg, thallium) in proportion to perfusion. This technique can be combined with stress testing. Radionuclide scanning is also used to evaluate tumors.

Variations

Single-photon emission CT (SPECT): SPECT uses a gamma camera that rotates around the patient. The resultant series of images are reconstructed by computer into 2-dimensional tomographic slices in a similar manner to that done in conventional CT. The 2-dimensional images can be used for tomographic reconstruction to yield a 3-dimensional image.

Disadvantages

Radiation exposure depends on the radio-nuclide and dose used. Effective doses tend to range from 1.5 to 17 mSv—eg, about 1.5 mSv for lung scans, about 3.5 to 4.5 mSv for bone and hepatobiliary scans, and about 17 mSv for technetium sestimibi heart scans. Reactions to radionuclides are rare.

The area that can be imaged accurately is limited because only signals near the gamma camera's face can be accurately localized. Image detail may also be limited.

Often, imaging must be delayed for up to several hours to give the radionuclide time to reach the target tissue.

Positron Emission Tomography

PET, a type of radionuclide scanning, uses compounds containing radionuclides that decay by releasing a positron (the positively charged antimatter equivalent of an electron). The released positron combines with an electron and produces 2 photons whose paths are 180° apart. Ring detector systems encircling the positron-emitting source simultaneously detect the 2 photons to localize the source. Because PET incorporates positron-emitting radionuclides into metabolically active compounds, it can provide information about tissue function.

Fluorine-18 [^{18}F]-labeled deoxyglucose (FDG) is used most commonly in clinical PET. FDG is an analog of glucose, and its uptake is proportional to glucose metabolic rates. A patient's relative glucose metabolic rate (called the standardized uptake value [SUV]) is calculated: The amount of FDG taken up from the injected dose is divided by the patient's body weight.

Uses

PET has several clinical indications, such as

- Cancer (eg, staging and evaluating specific types of cancer and evaluating response to treatment),

which accounts for about 80% of PET usage

• Cardiac function (eg, evaluating myocardial viability, detecting hibernating myocardium)

• Neurologic function (eg, evaluation of dementia and seizures)

PET applications continue to be investigated, although it is important to determine which applications are reimbursable.

Variations

PET-CT: Functional information provided by PET is superimposed on anatomic information provided by CT.

Disadvantages

The typical effective radiation dose during PET is about 7 mSv. The effective radiation dose with PET-CT is 5 to 18 mSv.

Production of FDG requires a cyclotron. FDG has a short half-life (110 min); thus, shipment from the manufacturer and completion of the scan must occur very rapidly. The resulting expense, inconvenience, and impracticality greatly limit the availability of PET.

Ultrasonography

In ultrasonography, a signal generator is combined with a transducer. Piezoelectric crystals in the signal generator convert electricity into high-frequency sound waves, which are sent into tissues. The tissues scatter, reflect, and absorb the sound waves to various degrees. The sound waves that are reflected back (echoes) are converted into electric signals. A computer analyzes the signals and displays the information on a screen.

Ultrasonography is portable, widely available, and safe. No radiation is used.

Variations

Ultrasound information can be displayed in several ways.

A-mode: This display mode is the simplest; signals are recorded as spikes on a graph. The vertical (Y) axis of the display shows the echo amplitude, and the horizontal (X) axis shows depth or distance into the patient. This type of ultrasonography is used for ophthalmologic scanning.

B-mode (gray-scale): This mode is most often used in diagnostic imaging; signals are displayed as a 2-dimensional anatomic image. B-mode is commonly used to evaluate the developing fetus and to evaluate organs, including the liver, spleen, kidneys, thyroid gland, testes, breasts, and prostate gland. B-mode ultrasonography is fast enough to show real-time motion, such as the motion of the beating heart or pulsating blood vessels. Real-time imaging provides anatomic and functional information.

M-mode: This mode is used to image moving structures; signals reflected by the moving structures are converted into waves that are displayed continuously across a vertical axis. M-mode is used primarily for assessment of fetal heartbeat and in cardiac imaging, most notably to evaluate valvular disorders.

Doppler: This type of ultrasonography is used to assess blood flow. Doppler ultra-sonography uses the Doppler effect (alteration of sound frequency by reflection off a moving object). The moving objects are RBCs in blood.

Direction and velocity of blood flow can be determined by analyzing changes in the frequency of sound waves:

- If a reflected sound wave is lower in frequency than the transmitted sound wave, blood flow is away from the transducer.
- If a reflected sound wave is higher in frequency than the transmitted sound wave, blood flow is toward the transducer.
- The magnitude of the change in frequency is proportional to blood flow velocity.

Changes in frequency of the reflected sound waves are converted into images showing blood flow direction and velocity.

Duplex Doppler ultrasonography combines the graphic display of spectral ultra-sonography with the images of B-mode. For color Doppler ultrasonography, color is superimposed on a gray-scale anatomic image. The color indicates direction of blood flow. By convention, red indicates flow toward and blue indicates flow away from the transducer.

Doppler ultrasonography is also used to evaluate vascularity of tumors and organs, to evaluate heart function (eg, as for echocardiography), to detect occlusion and stenosis of blood vessels, and to detect blood clots in blood vessels (eg, in deep venous thrombosis).

Disadvantages

Quality of images depends on the skills of the operator. Obtaining clear images of the target structures can be technically difficult in overweight patients.

Ultrasonography cannot be used to image through bone or gas, so certain images may be difficult to obtain.

Chapter 344. Complementary and Alternative Medicine

Introduction

(See also Ch. 345.)

Complementary and alternative medicine (CAM) refers to healing approaches and therapies that are not based on principles of mainstream, conventional medicine.

- **Complementary medicine** refers to unconventional practices used with mainstream medicine.

- **Alternative medicine** refers to unconventional practices used instead of mainstream medicine.

- **Integrative medicine** is health care that uses all appropriate therapeutic approaches—conventional and alternative—within a framework that focuses on the therapeutic relationship and the whole person.

CAM has been widely used in the US for decades. Almost 40% of adults use some form of CAM, most often to treat pain or anxiety or to modify cholesterol levels. Use is also common among patients with chronic pain, cancer, hepatitis C, or other intractable conditions. The most frequently used therapies include medicinal herbs and other plant-derived supplements (botanicals), mind-body practices, and massage therapy.

Some CAM therapies are now offered in hospitals and are sometimes reimbursed by insurance companies. Some traditional medical schools, including 45 North American medical schools in the Consortium of Academic Health Centers for Integrative Medicine, provide education about CAM and integrative medicine.

Broad, philosophic differences distinguish conventional and alternative approaches to healing (see Table 344-1).

Because patients worry about being criticized, they do not always volunteer information about their use of CAM to physicians. Therefore, it is very important for physicians to specifically ask their patients about CAM use in an open, nonjudgmental way. Learning about patients' use of CAM can strengthen rapport, build trust, and provide an opportunity to discuss CAM's benefits and risks. Physicians may also identify and avoid potentially harmful interactions between drugs and CAM therapies or nutritional supplements, monitor patient progress, guide patients to certified or licensed CAM practitioners, and learn from patients' experiences with CAM.

Efficacy

In 1992, the Office of Alternative Medicine in the National Institutes of Health (NIH) was formed to study the efficacy and safety of alternative therapies. In 1998, this office became the National Center for Complementary and Alternative Medicine (NCCAM; see www.nccam.nih.gov/). Other NIH offices (eg, National Cancer Institute) also fund some CAM research.

There are 3 types of support for CAM therapies:

- Use over periods of time ranging from decades to centuries

- Evidence of established physiologic mechanisms of action (eg, modification of γ-aminobutyric acid [GABA] activity in the brain by valerian)

- Efficacy as shown in clinical trials

A substantial amount of information about CAM is available in peer-reviewed publications, evidence-based reviews, expert panel consensus documents, and authoritative text-books; much of it has been published in languages other than English (eg, German, Chinese). However, most CAM therapies have not been tested in definitive clinical trials and probably will not be for the following reasons:

• Industry has no financial incentive to fund research.

• CAM therapies may be difficult to study using conventional methodology.

• Manufacturers of CAM products do not have to prove disease-specific efficacy.

Thus, the FDA allows marketing of dietary supplements and use of CAM devices but significantly restricts efficacy claims. Generally, manufacturers of dietary supplements can claim benefit to the body's structure or function (eg, improves cardiovascular health) but not benefit for treating disease (eg, treats hypertension).

Research: Designing studies of CAM therapies poses challenges beyond those faced by researchers of conventional therapies:

• Therapies may not be standardized. For example, there are different systems of acupuncture, and the contents and biologic activity of extracts made from the same plant species vary widely (chemical identification

[Table 344-1. Differences Between Conventional and Alternative Medicine]

and standardization of active ingredients is not considered part of CAM).

• Diagnoses may not be standardized; use of many CAM therapies (eg, traditional herbal medicine, homeopathy, acupuncture) is based on the patient's unique characteristics rather than on a specific disease or disorder.

• Double- or single-blinding is often difficult or impossible. For example, patients cannot be blinded as to whether they are practicing meditation. Reiki practitioners cannot be blinded as to whether or not they are using energy healing.

• Outcomes are difficult to standardize because they are often specific to the individual rather than objective and uniform (as mean arterial pressure, Hb A_{1C} level, and mortality are).

• Placebos may be difficult to devise because identifying the effective component of a CAM therapy may be difficult. For example, in massage, the effective component could be touching, the specific area of the body massaged, the particular massage technique used, or time spent with the patient.

From a conventional research perspective, use of a placebo control is particularly important when subjective outcomes (eg, pain, nausea, indigestion) are used and when disorders that are intermittent, self-limited, or both (eg, headaches) are being studied; such end points and disorders are often the targets of CAM therapies. However, CAM systems interpret placebo effects as nonspecific healing effects that arise out of the therapeutic interaction and are inseparable from specific treatments. In practice, alternative therapies are intended to optimize the patient's capacity for self-healing (placebo response) as well as treatment-specific effects. Thus, many CAM practitioners strive to enhance the quality of the healing environment and therapeutic relationship. Studying the effective components of a CAM therapy without undermining the integrity of that therapy in a research setting remains a methodologic challenge.

Safety

Although the safety of most CAM therapies has not been studied in clinical trials, many of these therapies have a good safety record. Many CAM therapies (eg, nontoxic botanicals, mind-body techniques such as meditation and yoga, body-based practices such as massage) have been used for thousands of years with no evidence of harm, and many seem to have no potential for harm. However, there are some safety considerations, including the following:

• Use of an alternative approach to treat a life-threatening disorder that can be effectively treated conventionally (eg, meningitis, diabetic ketoacidosis, acute leukemia)—perhaps the greatest risk of

CAM, rather than the risk of direct harm from a CAM therapy

- Toxicity from certain herbal preparations (eg, hepatotoxicity from pyrrolizidine alkaloids, *Atractylis gummifera*, chaparral, germander, greater celandine, Jin Bu Huan, kava, pennyroyal, or others; nephrotoxicity from *Aristolochia*; adrenergic stimulation from ephedra)

- Contamination (eg, heavy metal contamination of some Chinese and Ayurvedic herbal preparations; contamination of other products, such as PC-SPES and some Chinese herbs, with other drugs)

- Interactions between CAM therapies (eg, botanicals, micronutrients, other dietary supplements) and other drugs (eg, induction of cytochrome P-450 [CYP3A4] enzymes by St. John's wort, resulting in reduced activity of antiretrovirals, immunosuppressants, and other drugs), particularly when the drug has a narrow therapeutic index

- As with any physical manipulation of the body (including mainstream techniques such as physical therapy), injury (eg, nerve or cord damage due to spinal manipulation in patients at risk, bruising in patients with bleeding disorders)

Current alerts about harmful dietary supplements are available at the FDA web site. Historically, the FDA did not tightly regulate the production of dietary supplements. However, new FDA regulations now require compliance with manufacturing practices that guarantee quality and safety of supplements.

To help prevent injuries due to physical manipulations, patients should look for CAM practitioners who graduated from accredited schools and are professionally licensed. Rates of complications are very low when chiropractic or acupuncture is provided by practitioners with full credentials.

Categories

Five categories of alternative medicine are generally recognized (see Table 344-2):

- Alternative whole medical systems

- Mind-body medicine

- Biologically based practices

- Manipulative and body-based practices

- Energy medicine

The name of many therapies only partially describes their components.

Alternative Whole Medical Systems

Alternative medical systems are complete systems with explanation of disease, diagnosis, and therapy.

Ayurveda

Ayurveda, the traditional medical system of India, originated > 4000 yr ago. It is based on the theory that disease results from an imbalance of the body's life force (prana). The balance of prana is determined by equilibrium of the 3 bodily qualities (doshas): vata, pitta, and kapha. Most people have a dominant dosha; the specific balance is unique to each person.

Evidence: Few well-designed studies of Ayurvedic practices have been done. Use of Ayurvedic herbal combinations to relieve symptoms in patients with RA and to treat diabetes is being studied.

Uses: After determining the balance of doshas, practitioners design a treatment specifically tailored to

each patient. Ayurveda uses diet, herbs, massage, meditation, yoga, and therapeutic detoxification (panchakarma)—typically with enemas, oil massages, or nasal lavage—to restore balance within the body and with nature.

Possible adverse effects: In some of the herbal combinations used, heavy metals (mainly lead, mercury, and arsenic) are included because they are thought to have therapeutic effects. Cases of heavy metal toxicity have been reported.

Homeopathy

Developed in Germany in the late 1700s, homeopathy is based on the principle that like cures like. A substance that, when given in large doses, causes a certain set of symptoms is believed to cure the same symptoms when it is given in minute doses. The minute dose is thought to stimulate the body's healing mechanisms. Treatments are based on the patient's unique characteristics, including personality and lifestyle, as well as symptoms and general health.

Remedies used in homeopathy are derived from naturally occurring substances, such as plant extracts and minerals. Extremely low concentrations are prepared in a specific way. The more dilute the homeopathic remedy, the stronger it is considered to be.

Some solutions are so dilute that they contain no molecules of the active ingredient. There is no compelling, scientific explanation for how these dilutions could work.

Evidence: Efficacy of homeopathic remedies for various disorders has been studied. No study has clearly shown efficacy for any specific homeopathic remedy, although some studies have shown positive results (eg, one well-conducted, randomized, placebo-controlled clinical study showed a therapeutic benefit greater than placebo in the treatment of diarrhea in children). Homeopathy is commonly incorporated into health care practices in Europe and India.

[Table 344-2. Types of Alternative Medicine]

Uses: Homeopathy has been used to treat various disorders, such as allergies, rhinitis, digestive problems, musculoskeletal pain, and vertigo. The effect of homeopathic solutions on joint pain and tenderness and quality of life in fibromyalgia is being studied.

Possible adverse effects: Homeopathy is well-tolerated and has few risks; rarely, an allergic or toxic reaction occurs.

Unlike herbal and nutritional supplements, homeopathic remedies are regulated by the FDA as drugs; they are available over the counter or by prescription. Because so little active ingredient is left after dilution, active ingredients are tested before dilution. Homeopathic remedies have been temporarily exempted from limits on the amount of alcohol (the usual diluent) that they can contain. However, the label is required to list the following:

• Manufacturer

• The label "homeopathic"

• At least one indication

• Instructions for safe use

• Unless specifically exempted, the active ingredient and degree of dilution

Conventional clinicians should not assume that a homeopathic remedy taken by a patient is biologically inactive. Patients often use the term homeopathic erroneously in reference to a dietary supplement they are taking. Also, the FDA allows many medicinal herbs to be registered and labeled as homeopathic if they undergo a particular pharmaceutical process.

Naturopathy

This therapy began as a formal health care system in the US during the early 1900s. Founded on the healing power of nature, naturopathy emphasizes prevention and treatment of disease through a healthy lifestyle, treatment of the whole patient, and use of the body's natural healing abilities. This system also focuses on finding the cause of a disease rather than merely treating symptoms. Some of this system's principles are not that different from those of traditional healing systems such as Ayurveda and traditional Chinese medicine.

Naturopathy uses a combination of therapies, including acupuncture, counseling, exercise therapy, medicinal herbs, homeopathy, hydrotherapy, natural childbirth, nutrition, physical therapies (eg, heat or cold therapy, ultrasound, massage), guided imagery, and stress management.

Traditional Chinese Medicine

Originating > 2000 yr ago, traditional Chinese medicine is based on the theory that disease results from improper flow of the life force (qi). The movement of qi is restored by balancing the opposing forces of yin and yang, which manifest in the body as heat and cold, external and internal, and deficiency and excess. Various practices (eg, acupuncture, diet, massage, medicinal herbs, meditative exercise called qi gong) are used to preserve and restore qi and thus health.

Evidence: Chinese medicine traditionally uses formulas containing mixtures of herbs to treat various disorders. Traditional formulas can be studied; for example, efficacy in the treatment of irritable bowel syndrome has been shown. One herb, used by itself, may not be as effective and may have side effects. Nevertheless, current conventional research favors study of single herbs. For example, *Tripterygium wilfordii* (thunder god vine) has demonstrated anti-inflammatory properties and clinical efficacy in treating RA, and *Astragalus* may benefit patients with lung cancer. Various Chinese herbs have been studied as treatments for hepatitis and hepatic fibrosis. Some studies suggest efficacy, but data are limited.

Possible adverse effects: One problem is the standardization and quality control of Chinese herbs. Many are unregulated in Asia; they may be contaminated with heavy metals from polluted ground water or may be adulterated with drugs such as antibiotics or corticosteroids. However, high-quality products are available through certain manufacturers that comply with FDA Good Manufacturing Practices.

Mind-Body Medicine

Mind-body medicine is based on the theory that mental and emotional factors influence physical health through a system of neuronal, hormonal, and immunologic connections throughout the body. Behavioral, psychologic, social, and spiritual techniques are used to preserve health and to prevent or cure disease.

Because scientific evidence supporting the benefits of mind-body medicine is abundant, many of these approaches are now considered mainstream, although they remain underused. Techniques such as biofeedback, guided imagery, hypnotherapy, meditation, and relaxation are used in the treatment of chronic pain, coronary artery disease, headaches, insomnia, and incontinence and as aids during childbirth. These techniques are also used to help patients cope with disease-related and treatment-related symptoms of cancer and to prepare patients for surgery. Efficacy of mind-body medicine in patients with asthma, hypertension, or tinnitus is not as clear.

Biofeedback

For this technique, electronic devices are used to provide information to patients about biologic functions (eg, heart rate, BP, muscle activity, skin temperature, skin resistance, brain surface electrical activity).

Uses: With the help of a therapist or with training, patients can then use information from biofeedback to modify the function or to relax, thereby lessening the effects of conditions such as pain, stress, insomnia, and headaches. Biofeedback is also used in patients with fecal or urinary incontinence, chronic abdominal pain, tinnitus, Raynaud's syndrome, or attention or memory disorders (eg, attention-

deficit/hyperactivity disorder, traumatic brain injury). Generally, biofeedback does not seem to be useful in asthma; a possible exception is heart rate variability biofeedback, which may help reduce asthma symptoms and drug use and improve pulmonary function.

Guided imagery

Mental images, self-directed or guided by a practitioner, are used to help patients relax (eg, before a procedure) and to promote wellness and healing (to try to effect physical changes—eg, by mobilizing the immune system). The images can involve any of the senses.

Uses: Imagery used with relaxation techniques (muscle relaxation and deep breathing) may help reduce pain and improve quality of life in patients with cancer. Imagery has also been used in patients with psychologic trauma.

Hypnotherapy

Hypnotherapy is derived from western psychotherapeutic practice. Patients are put into an advanced state of relaxation. They become absorbed in the images presented by the hypnotherapist and are relatively distracted from but not unconscious of their surroundings and the experiences they are undergoing. Some patients learn to hypnotize themselves.

Uses: Hypnotherapy is used to treat pain syndromes, phobias, and conversion disorders and has been used with some success to manage smoking cessation and weight loss. It can reduce pain and anxiety during medical procedures in adults and children. It may be useful in irritable bowel syndrome, headaches, asthma, and some skin disorders (eg, warts, psoriasis). It may help lower BP. Hypnotherapy helps control nausea and vomiting (particularly anticipatory) related to chemotherapy and is useful in palliative cancer care. Some evidence suggests that hypnotherapy helps lessen anxiety and improve quality of life in patients with cancer.

Meditation

In meditation, patients regulate their attention or systematically focus on particular aspects of inner or outer experience. The most highly studied forms of meditation are transcendental meditation (TM) and mindfulness meditation. Although research is incomplete, results to date suggest that meditation could work via at least 2 mechanisms:

- Producing a relaxed state that counters excessive activation of neurohormonal pathways resulting from repeated stress

- Developing the capacity for metacognitive awareness (the ability to stand back from and witness the contents of consciousness), thus theoretically helping patients not react to stress automatically (with highly conditioned, learned patterns of behavior) and helping them tolerate and regulate emotional distress better

Most meditation practices were developed in a religious or spiritual context; their ultimate goal was some type of spiritual growth, personal transformation, or transcendental experience. However, studies suggest that as a health care intervention, meditation can often be beneficial regardless of a person's cultural or religious background.

Uses: Meditation has been used to relieve anxiety, pain, depression, stress, insomnia, and symptoms of chronic disorders such as cancer or cardiovascular disorders. It is also used to promote wellness.

Relaxation Techniques

Relaxation techniques are practices specifically designed to relieve tension and strain. The specific technique may be aimed at

- Reducing activity of the sympathetic nervous system

• Lowering BP

• Easing muscle tension

• Slowing metabolic processes

• Altering brain wave activity

Relaxation techniques may be used with other techniques, such as meditation, guided imagery, or hypnotherapy.

Biologically Based Practices

Biologically based practices use naturally occurring substances and include biologic therapies (eg, shark cartilage to treat cancer, glucosamine to treat osteoarthritis), diet therapies, herbalism (see p. 3421), orthomolecular medicine, and chelation therapy.

Diet Therapy

Diet therapy uses specialized dietary regimens (eg, Gerson therapy, macrobiotic diets, Pritikin diet) to treat or prevent a specific disorder (eg, cancer, cardiovascular disorders) or generally promote wellness. Some diets (eg, Mediterranean diet) are widely accepted and encouraged in traditional western medicine. The Ornish diet, a very low-fat vegetarian diet, can help reverse arterial blockages that cause coronary artery disease and may help prevent or slow the progression of prostate and other cancers. Some people following a macrobiotic diet have reported cancer remission, but a well-controlled clinical study has not been conducted. Because it usually takes months or years for benefits to be realized, diet therapy is more likely to be effective if started early.

Orthomolecular Medicine

Orthomolecular medicine, also called nutritional medicine, aims to provide the body with optimal amounts of substances that naturally occur in the body. Nutrition is the focus in diagnosis and treatment.

This therapy differs from diet therapy because it uses supradietary doses of individual micronutrients. High doses of vitamins, minerals, enzymes, hormones (eg, melatonin), amino acids, or various combinations may be used. Practitioners believe that people's nutritional needs far exceed the recommended daily allowances and that nutritional therapy must be individualized based on each patient's medical profile. High doses of micro-nutrients are also used as biologic response modifiers in an attempt to modulate inflammation and other disease processes. Doses may be administered orally or, far less often, intravenously.

Evidence and uses: Treatment claims include benefit for a wide range of disorders (eg, cancer, cardiovascular disease, chronic fatigue, chronic pain, autism, psychiatric disorders). These treatments are widely used, and many patients report clinical improvement. However, no clinical study data support the usefulness of most of these practices. Exceptions include use of high-dose fish oils to treat hypertriglyceridemia (and possibly inflammatory and mood disorders), use of high-dose antioxidants to prevent macular degeneration, and possibly high-dose melatonin to prevent or treat cancer. If sufficient evidence of usefulness is shown, treatments (eg, high-dose fish oils to treat hypertriglyceridemia, high-dose antioxidants to prevent macular degeneration) become part of conventional medicine.

Possible adverse effects: Clinicians should be aware that high-dose micronutrients may cause harm; eg, some micronutrients may increase the risk of developing prostate cancer or blunt the effects of certain cancer treatments.

Chelation Therapy

In chelation therapy, a drug is used to bind with and remove hypothesized excess or toxic amounts of a

metal or mineral (eg, lead, copper, iron, calcium) from the bloodstream. In conventional medicine, chelation therapy is a widely accepted way to treat lead and other heavy metal poisoning (see p. 3344). Chelation therapy with EDTA (ethylene diamine tetraacetic acid) has also been suggested as a way to remove calcium and thus treat atherosclerosis; whether this use is safe and effective has not been proved but is under study.

Manipulative and Body-Based Practices

Manipulative and body-based practices include chiropractic, massage therapy, postural reeducation, reflexology, and structural integration.

Chiropractic

In chiropractic, the relationship between the structure of the spine and function of the nervous system is thought to be the key to maintaining or restoring health. The main method for restoring this relationship is spinal manipulation. Chiropractors may also provide physical therapies (eg, heat and cold, electrical stimulation, rehabilitation strategies), massage, or acupressure and may recommend exercises or lifestyle changes.

Uses: Chiropractic provides short-term relief of low back pain, but continuing adjustments may not provide additional benefit. Thus, the usefulness of chiropractic for chronic back pain is unclear. Chiropractic is sometimes useful in treating headache disorders (although data are inconsistent) and nerve impingement syndromes; it has also been used to treat neck pain. The usefulness of manipulation for conditions not directly related to the musculoskeletal system has not been established.

Possible adverse effects: Serious complications resulting from spinal manipulation (eg, low back pain, damage to cervical nerves, damage to arteries in the neck) are rare. Spinal manipulation is not recommended for patients with osteoporosis or symptoms of neuropathy (eg, paresthesias, loss of strength in a limb). Whether it is safe for patients who have had spinal surgery or stroke or who have a vascular disorder is unclear.

Massage Therapy

In massage therapy, body tissues are manipulated to promote wellness and reduce pain and stress. The therapeutic value of massage for many musculoskeletal symptoms and stress is widely accepted. Massage has been shown to help relieve the following:

• Muscle soreness

• Pain due to back injuries

• Fibromyalgia

• Anxiety, fatigue, pain, nausea, and vomiting in cancer patients

Massage therapy is reported to be effective in treating low birth weight infants, preventing injury to the mother's genitals during childbirth, relieving chronic constipation, and controlling asthma.

Massage can cause bruising and bleeding in patients with thrombocytopenia or bleeding disorders. Therapists must avoid putting pressure on bones affected by osteoporosis or metastatic cancer.

Reflexology: This variant of massage therapy relies on manual pressure applied to specific areas of the foot; these areas are believed to correspond to different organs or body systems via meridians. Stimulation of these areas is believed to eliminate the blockage of energy responsible for pain or disease in the corresponding body part. Reflexology may help relieve anxiety in patients with cancer.

Structural integration: Structural integration is based on the theory that good health depends on correct body alignment. It is a form of deep tissue manipulation that is typically done over a series of sessions.

Correct alignment of bone and muscle is achieved by manipulating and stretching muscles and fascia. The efficacy has not been proved.

Other Therapies

Several lesser known therapies are used in various cultures. They include cupping, scraping (eg, coining, spooning), and moxibustion. Some of these therapies result in lesions that may be mistaken for signs of child abuse. These therapies are thought to stimulate the body's energy and to enable toxins to leave the body.

Cupping: This therapy is used in traditional Chinese medicine and in Middle Eastern, Asian, Latin American, and Eastern European cultures. The air inside a cup is heated, often using a cotton ball soaked in alcohol, then ignited. The heated cup is immediately inverted and placed on the skin. The resulting vacuum sucks the skin partway into the cup, which may be left in place for several minutes. Cupping has been used to treat bronchitis, asthma, digestive disorders, and certain types of pain; however, no research has verified its efficacy. Cupping may redden or burn the skin.

Scraping: This therapy involves rubbing an implement across lubricated (oiled or wet) skin, usually on the back, neck, and shoulders. Coining uses a coin; spooning uses a spoon. These therapies are used to treat the common cold, influenza, muscle pain and stiffness, and other disorders. Coining results in linear red marks; spooning results in ecchymosis.

Moxibustion: Dried moxa herb (a mugwort) is burned usually just above but sometimes directly on the skin over acupuncture points. The herb may be in the form of incense sticks. This therapy is used to treat fever, digestive problems, and pain due to injury or arthritis. Moxibustion can result in circular burns (which resemble burns from cigarette tips) and vesicobullous lesions.

Energy Medicine

Energy medicine intends to manipulate subtle energy fields (also called biofields) thought to exist in and around the body. All energy therapies are based on the belief that a universal life force or subtle energy resides in and around the body. Qi gong, which is used in traditional Chinese medicine, is an energy therapy.

Acupuncture

Acupuncture, a therapy within traditional Chinese medicine, is one of the most widely accepted alternative therapies in the western world. Specific points on the body are stimulated, usually by inserting thin needles into the skin and underlying tissues. Stimulating these specific points is believed to unblock the flow of qi along energy pathways (meridians) and thus restore balance; > 350 defined points are located along the meridians. The procedure is generally not painful but may cause a tingling sensation. Sometimes stimulation is increased by twisting or warming the needle. Acupuncture points may also be stimulated by pressure (called acupressure), lasers, ultrasound, or a very low voltage electrical current (called electroacupuncture) applied to the needle.

Evidence and uses: Research has shown that acupuncture releases various neurotransmitters (eg, endorphins) that act as natural painkillers. Reasonable evidence supports the efficacy of acupuncture as a pain reliever, an antinauseant, and an antiemetic. However, in many studies, results of sham acupuncture are comparable to those of actual acupuncture; the relative efficacy of sham and actual acupuncture is still not clear.

Acupuncture relieves nausea and vomiting related to surgery and chemotherapy. When used with antiemetic drugs, acupuncture has an additive effect. Acupuncture also helps relieve nausea and vomiting during pregnancy. Acupuncture has been used to relieve pain after surgical or dental procedures. As part of a comprehensive treatment plan (sometimes as adjunctive treatment), acupuncture may be useful in treating addiction, carpal tunnel syndrome, fibromyalgia, headache, low back pain, osteoarthritis, and xerostomia (in patients with advanced cancer) and in stroke rehabilitation.

Preliminary evidence suggests that acupuncture may relieve vasomotor symptoms in men taking gonadotropin analogs for prostate cancer. The evidence for relieving symptoms and improving pulmonary function in patients with asthma and for relieving pain or improving function in patients with RA is mixed. Acupuncture is ineffective for smoking cessation and weight loss.

Possible adverse effects and contraindications: Adverse effects are rare if the procedure is done correctly. Worsening of symptoms (usually temporary) and vasovagal symptoms are the most common. Because acupuncture can cause fainting and drowsiness (although rarely), patients should be supine at least for their first treatment and should not drive or do any tasks that require alertness after treatment until they know how it affects them. Infection is extremely rare; most practitioners use disposable needles.

Acupuncture is contraindicated in patients with severe bleeding disorders. Electroacupuncture is contraindicated in patients with a pacemaker or an implanted defibrillator. Acupuncture at certain points may stimulate uterine contractions, and in traditional Chinese medicine, it is used to modulate labor. Only specially trained practitioners should use acupuncture in pregnant women.

Magnets

Energy therapy may rely on magnetic (alternating- or direct-current) fields.

Evidence and uses: Magnets, in particular, are a popular treatment for various musculoskeletal disorders, although multiple studies have shown no effectiveness, especially for pain relief, one of their most common applications.

Preliminary evidence suggests that static (permanent) magnets may help relieve pain in patients with osteoarthritis. However, the evidence that electromagnets may reduce pain and improve physical function is more consistent than that for static magnets. Using pulsating electromagnetic fields to speed healing of nonunion fractures is well-established.

Possible contraindications: Possible contraindications for magnets include pregnancy (effects on the fetus are unknown) and use of implanted cardiac devices, an insulin pump, or a drug given by patch.

Therapeutic Touch

Therapeutic touch, sometimes referred to as laying on of hands, uses the therapist's healing energy to identify and repair imbalances in a patient's biofield. Usually, practitioners do not touch the patient; instead, they move their hands back and forth over the patient. Therapeutic touch has been used to lessen anxiety and improve the sense of well-being in patients with cancer, but these effects have not been rigorously studied. In the US, nurses have introduced therapeutic touch into ICUs and other hospital settings.

Reiki: Reiki, which originated in Japan, is a similar technique; in Reiki, practitioners channel energy through their hands and transfer it into the patient's body to promote healing. Practitioners are thought to have special healing powers, which are required for these treatments.

Chapter 345. Dietary Supplements

Introduction

(See also Ch. 344.)

Dietary supplements are the most commonly used of all complementary and alternative therapies, primarily because they are widely available and can be bought without consulting a health care practitioner.

The FDA regulates dietary supplements differently from drugs. The FDA regulates only quality control and good manufacturing processes but does not ensure standardization of the active ingredients or efficacy.

Definition: The Dietary Supplement Health Education Act (DSHEA) of 1994 defines a dietary supplement as

- Any product (except tobacco)—in pill, capsule, tablet, or liquid form—containing a vitamin, mineral, herb or other plant product, amino acid, or other known dietary substance that is intended as a supplement to the normal diet

In addition, certain hormones, such as dehydroepiandrosterone (DHEA, a precursor to androgens and estrogens) and melatonin, are regulated as dietary supplements and not as prescription drugs.

Labeling: The DSHEA requires that the product label identify the product as a dietary supplement and notify the consumer that the claims for the supplement have not been evaluated by the FDA. The label must also list each ingredient by name, quantity, and total weight and identify plant parts from which ingredients are derived . Manufacturers are permitted to make claims about the product's structure and function (eg, good for urinary tract health) but cannot make or imply claims for the product as a drug or therapy (eg, treats UTIs).

Safety and efficacy: Most people who use dietary supplements assume that they are good for health generally, are safe and effective for treating specific conditions, or both because dietary supplements are natural (ie, derived from plants or animals) and because some are supported by centuries of use in traditional systems of medicine. However, the FDA does not require manufacturers of dietary supplements to prove safety or efficacy (although supplements must have a history of safety). Most supplements have not been rigorously studied. For most, evidence suggesting safety or efficacy comes from traditional use, in vitro studies, certain case reports, and animal studies. However, manufacturers and distributors of supplements now must report serious adverse events to the FDA through the MedWatch system. There are a few supplements (eg, fish oil, chondroitin/glucosamine, saw palmetto) now proved to be safe and useful complements to standard drugs.

Evidence concerning the safety and efficacy of dietary supplements is increasing rapidly as more and more clinically based studies are being done. Information about such studies is available at the National Institutes of Health's National Center for Complementary and Alternative Medicine (NCCAM) web site (www.nccam.nih.gov/research/clinicaltrials/).

Purity and standardization: Lack of regulation and government monitoring also means that supplements are not monitored to ensure that they contain the ingredients or amount of active ingredient the manufacturer claims they contain. The supplement may have un-listed ingredients, which may be inert or harmful (eg, natural toxins, bacteria, pesticides, lead or other heavy metals), or it may contain variable amounts of active ingredients, especially when whole herbs are ground or made into extracts. Consumers are at risk of getting less, more, or, in some cases, none of the active ingredient, if the active ingredient is even known. Most herbal products are mixtures of several substances, and which ingredient is the most active is not always known. The lack of standardization means not only that products from different manufacturers may vary, but also that different batches produced by the same manufacturer may differ. This product variability is a particular source of difficulty in conducting rigorous scientific trials and comparing the results among different trials. However, some supplements have been standardized and may include a designation of standardization on the label.

New regulations governing supplement production in the US include rules for Good Manufacturing Practices (GMPs). These rules strengthen standards for keeping manufacturing facilities and equipment clean and raw materials pure and uncontaminated. GMPs also ensure proper labeling, packaging, and storage of the finished product.

Other concerns: Additional areas of concern include

• Use of dietary supplements instead of conventional drugs

• Stability of supplements (especially herbal products) once manufactured

• Toxicity

• Interactions between supplements and drugs

Most information about these concerns comes from sporadic individual reports (see Table 345-1) and some references.

Despite these concerns, many patients strongly believe in the benefits of supplements and continue to use them with or without a physician's involvement. Patients may not think to disclose or may wish to conceal their use of dietary supplements. For this reason, the outpatient history should periodically include explicit questions about past

[**Table 345-1.** Some Possible Dietary Supplement-Drug Interactions*]

and new use of complementary and alternative therapies, including dietary supplements. Many physicians incorporate some supplement use into their practice; their reasons include proven benefit of the supplement, a desire to ensure that supplements are used safely by patients who will use supplements anyway, and the physician's belief that the supplements are safe and effective. There are few data to guide patient counseling regarding supplement safety. But some experts believe that the overall number of problems due to dietary supplements is rare compared with the overall number of doses taken and that the supplement, if correctly manufactured, is likely to be safe. As a result, these experts advise purchase of supplements from a well-known manufacturer, and many recommend buying supplements made in Germany because there they are regulated as drugs and thus oversight is stricter than in the US.

The following supplements are ones that are most popular, are effective, or have some questions about their safety. More complete information is available through the NCCAM web site (www.nccam.nih.gov/).

Black Cohosh

Black cohosh is the underground stem of a plant that can be ingested directly in powdered form or extracted into tablet or liquid form. It should be standardized to contain certain triterpenes. Black cohosh contains no phytoestrogens that can account for its purported estrogen-like effects, but it contains small amounts of anti-inflammatory compounds, including salicylic acid.

Claims: Black cohosh is said to be useful for menopausal symptoms (eg, hot flushes, mood lability, tachycardia, vaginal dryness), for menstrual symptoms, and for arthralgias in RA or osteoarthritis.

Scientific evidence regarding benefit in relieving menstrual symptoms is conflicting. There are few reliable data on its effectiveness for other disorders and symptoms.

Adverse effects: Adverse effects are uncommon. The most likely are headache and GI distress. Dizziness, diaphoresis, and hypotension (if high doses are taken) may occur.

There is no evidence that black cohosh interferes with any drugs. Theoretically, black cohosh is contraindicated in patients with aspirin sensitivity, liver disease, hormone-sensitive cancers (eg, certain

kinds of breast cancer), stroke, or high BP. The US Pharmacopeia (USP) has recommended that black cohosh products be labeled with a warning declaring that they may be hepatotoxic.

Chamomile

The flower of chamomile is dried and drunk as a tea or used topically as an extract.

Claims: Chamomile tea is said to reduce inflammation and fever, to act as a mild sedative, to relieve stomach cramps and indigestion, and to promote healing of gastric ulcers. Chamomile extract applied topically in a compress is said to soothe irritated skin. Mechanism is due to essential oil containing bisabolol constituents.

Adverse effects: Chamomile is generally safe. It may interact with alcohol and sedatives (eg, barbiturates). Some people are allergic to pollen in chamomile products.

Chamomile may reduce the absorption of oral drugs. Chamomile may also increase the effects of anticoagulants and sedatives (including alcohol) and decrease the absorption of iron supplements.

Chondroitin Sulfate

Chondroitin sulfate is a glycosaminoglycan, a natural component of cartilage. It is extracted from shark or cow cartilage or manufactured synthetically. It is frequently combined with glucosamine.

Claims: Chondroitin sulfate is used to treat osteoarthritis. Scientific evidence shows no benefit when chondroitin sulfate is taken by itself. However, evidence suggests that in combination with glucosamine, it may reduce joint pain, improve joint mobility, and allow reduction of the doses of conventional anti-inflammatory drugs when it is taken for 6 to 24 mo. Effects over longer periods are unclear. Mechanism is unknown. Dose is 600 mg po once/day to 400 mg po tid.

Adverse effects: No serious adverse effects have been reported. Among the most common adverse effects are stomach pain, nausea, and other GI symptoms.

Chondroitin sulfate may also affect the action of warfarin. Chondroitin sulfate is safe for most people, but people who have asthma, blood-clotting disorders, or prostate cancer should use caution when taking it.

Chromium

Chromium, a trace mineral, potentiates the action of insulin. Sources include carrots, potatoes, broccoli, whole grains, and molasses. Picolinate is a by-product of tryptophan that is paired with chromium in supplements because it is said to help the body absorb chromium more efficiently.

Claims: Chromium picolinate is said to promote weight loss, build muscle, reduce body fat, lower cholesterol and triglyceride levels, and enhance insulin function. Although chromium deficiency impairs insulin function, there is no evidence that supplementation helps patients with diabetes, nor is there evidence that it benefits body composition or lipid levels.

Adverse effects: Some evidence suggests that chromium picolinate damages chromosomes and may cause cancer. Some forms of chromium may contribute to GI irritation and ulcers. Chromium supplements interfere with iron absorption.

Coenzyme Q10

Coenzyme Q10 (ubiquinone) is an antioxidant that is also a cofactor for mitochondrial ATP generation. The levels of coenzyme Q10 seem to be lower in older people and in people with chronic diseases, such as cardiac problems, cancer, Parkinson's disease, diabetes, HIV/AIDS, and muscular dystrophies. However, it is not known whether these low levels contribute to these disorders.

Claims: Coenzyme Q10 is said to be useful because of its antioxidant effect and role in energy

metabolism. Specific claims include an anticancer effect mediated by immune stimulation, decreased insulin requirements in patients with diabetes, slowed progression of Parkinson's disease, efficacy in treatment of heart failure, and protection against anthracycline cardiotoxicity. Although some preliminary studies suggest coenzyme Q10 may be useful in treating these disorders, results are unclear and more testing is needed.

Adverse effects: Coenzyme Q10 may decrease response to warfarin. There are case reports of GI symptoms (eg, loss of appetite, abdominal pain, nausea, vomiting) and CNS symptoms (eg, dizziness, photophobia, irritability, headache). Other adverse effects include itching, rash, fatigue, and flu-like symptoms. Coenzyme Q10 is not recommended for people who exercise vigorously.

Cranberry

Cranberries are fruit that can be consumed whole or made into food products such as jellies and juices.

Claims: People most often take cranberries to help prevent and relieve the symptoms of UTIs. The effectiveness of cranberries in preventing UTIs has been documented. Natural unprocessed cranberry juice contains anthocyanidins, which prevent *Escherichia coli* from attaching to the urinary tract wall.

Some people take cranberry juice to reduce fever and treat certain cancers; however, there is no scientific proof that it is effective for these uses.

Adverse effects: No adverse effects are known. However, because most cranberry juice is highly sweetened to offset its tart taste, people with diabetes should not consume cranberry juice unless it is artificially sweetened. Because cranberry increases urinary acidity, it may promote stone formation in patients with uric acid kidney stones. Cranberry products may increase the effects of warfarin.

Creatine

Phosphocreatine is a compound stored in muscle; it donates phosphate to ADP and thereby rapidly replenishes ATP during anaerobic muscle contraction. It is synthesized endogenously in the liver from arginine, glycine, and methionine. Dietary sources are milk, steak, and some fish.

Claims: Creatine is said to improve physical and athletic performance and to reduce muscle fatigue. Some evidence suggests creatine is effective at increasing work done in a short maximal effort (eg, sprinting, weightlifting). It has proven therapeutic use in muscle phosphorylase deficiency (glycogen storage disease type V [McArdle disease]) and gyrate atrophy of the choroid and retina; early data also suggest possible effects in Parkinson's disease and amyotrophic lateral sclerosis.

Adverse effects: Creatine may cause weight gain (possibly because of an increase in muscle mass) and spurious increases in serum creatinine levels. Minor GI symptoms, dehydration, electrolyte imbalance, and muscle cramps have been reported anecdotally.

Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) is a steroid produced by the adrenal gland and is a precursor of estrogens and androgens. Effects on the body are similar to those of testosterone. DHEA can also be synthesized from precursors in the Mexican yam; this form is the most commonly available.

Claims: DHEA supplements are said to improve mood, energy, sense of well-being, and the ability to function well under stress. They are also said to improve athletic performance, stimulate the immune system, deepen nightly sleep, lower cholesterol levels, decrease body fat, build muscles, reverse aging, improve brain function in patients with Alzheimer's disease, and increase libido. The medicinal claims of DHEA have not been proved.

Adverse effects: Adverse effects are unknown. There are theoretical risks of gynecomastia in men, hirsutism in women, and stimulation of prostate and breast cancer. There is a case report of mania and one of seizure.

Echinacea

Echinacea, a North American wildflower, contains a variety of biologically active substances.

Claims: Echinacea is said to stimulate the immune system. When taken at the start of a cold, it is said to shorten the duration of cold symptoms. Well-designed studies have not supported this effect. Topical preparations are used to promote wound healing.

Adverse effects: Most adverse effects are mild and transitory; they include dizziness, fatigue, headache, and GI symptoms. No other adverse effects are known. Theoretically, echinacea is contraindicated in patients with autoimmune disorders, multiple sclerosis, AIDS, TB, and organ transplants because it may stimulate T cells. Echinacea inhibits some cytochrome P-450 enzymes and stimulates others; it can therefore potentially interact with drugs metabolized by the same enzymes (eg, anabolic steroids, azole antifungals, methotrexate). Allergic reactions are possible in patients with pollen allergies.

Feverfew

Feverfew is a bushy perennial herb. The dried leaves are used in capsules, tablets, and liquid extracts. Parthenolides and glycosides are thought to be the components responsible for its purported anti-inflammatory effects and relaxant effects on smooth muscle.

Claims: Feverfew is said to be effective in the prevention of migraine headaches. Evidence from 3 of 4 relatively small but well-designed studies supports these claims, but the largest and best designed of these studies does not. Differences among study findings may reflect the different formulations of feverfew used.

Feverfew is also said to be useful for relieving menstrual pain, asthma, and arthritis. In vitro, feverfew inhibits platelet aggregation.

Adverse effects: Mouth ulcers, contact dermatitis, dysgeusia, and mild GI symptoms may occur. Abrupt discontinuation may worsen migraines and cause nervousness and insomnia. Feverfew is contraindicated in pregnant women; theoretically, it is contraindicated in patients taking other antimigraine drugs, iron supplements, NSAIDs, antiplatelet drugs, or warfarin.

Fish Oil

Fish oil may be extracted directly or concentrated and put in capsule form. Active ingredients are ω-3 fatty acids (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]). Western diets typically are low in ω-3 fatty acids.

Claims: Fish oil is used for prevention and treatment of atherosclerotic cardiovascular disease. Strong scientific evidence suggests that EPA/DHA 800 to 1500 mg/day reduces risk of MI and death due to arrhythmia in patients who have preexisting coronary artery disease and are taking conventional drugs. It also reduces triglycerides in a dose-dependent way (25 to 40% with EPA/DHA 4 g/day) and slightly lowers BP (2 to 4 mm Hg with EPA/DHA > 3 g/day). Mechanisms are probably multiple but unknown. Benefits are suspected but not yet proved for primary prevention of atherosclerotic cardiovascular disease, treatment of RA, and prevention of cyclosporine nephrotoxicity.

Adverse effects: Fishy eructation, nausea, and diarrhea may occur. Risk of bleeding increases with EPA/DHA > 3 g/day. Concerns about mercury contamination are not substantiated in laboratory testing. Even so, pregnant or breastfeeding women should not take ω-3 fatty acid supplements extracted from fish and should limit consumption of certain types and amounts of fish because of the potential risk of mercury contamination.

Garlic

Garlic bulbs are extracted and made into tablet form; the major active ingredient is allicin, an amino acid by-product.

Claims: Garlic is said to have favorable effects on several cardiac risk factors, including reduction of BP and serum lipid and glucose levels; garlic inhibits platelets in vitro. Garlic is also said to protect against laryngeal, gastric, colorectal, and endometrial cancer and adenomatous colorectal polyps. Scientific evidence shows limited to no protection against cancer. Garlic consumed in high doses has general antimicrobial effects.

Adverse effects: Breath and body smell and nausea may occur; high doses may cause burning in the mouth, esophagus, and stomach. Theoretically, garlic is contraindicated in patients who have bleeding diatheses or who take antihypertensives, antiplatelet drugs, or warfarin. Garlic can reduce serum saquinavir levels.

Ginger

Ginger root is extracted and made into tablet form. Active ingredients include gingerols (which give ginger its flavor and odor) and shogaols.

Claims: Ginger is said to be an effective antiemetic and antinauseant, especially for nausea caused by motion sickness or pregnancy, and to relieve intestinal cramps. Ginger is also used as an anti-inflammatory and analgesic. It may have antibacterial properties and antiplatelet effects in vitro, but data are inconsistent. Scientific studies are consistent with a beneficial effect in pregnancy-related nausea and vomiting.

Adverse effects: Ginger is usually not harmful, although some people have a burning sensation when they eat it. Nausea, dyspepsia, and dysgeusia are possible. Theoretically, ginger is contraindicated in patients who have bleeding diatheses or who take anti-platelet drugs or warfarin.

Ginkgo

Ginkgo (*Ginkgo biloba*) is prepared from leaves of the ginkgo tree (commonly planted in the US for ornamental purposes). Active ingredients are believed to be terpene ginkgolides and flavonoids.

The fruit of the gingko tree, which is quite malodorous, is not used in ginkgo products. Contact with the fruit pulp, which may be present under female ginkgo trees, can cause severe skin inflammation (dermatitis). The raw seeds of the fruit are toxic and can cause seizures and, in large amounts, death. Cooked ginkgo seeds are eaten in Asia and are available in Asian food shops in the US; because the seeds do not contain ginkgolides and flavonoids, they do not have therapeutic effects.

Claims: Strong scientific evidence supports use of ginkgo for symptomatic relief of claudication, although exercise and cilostazol may be more effective. Gingko increases the distance that affected people can walk without pain.

Ginkgo has long been used in people with dementia. Benefit in dementia seems unlikely based on a recent large clinical trial in which ginkgo was not effective in reducing the development of dementia and Alzheimer's disease in older people. However, a previous large US clinical trial indicated that ginkgo temporarily stabilized mental and social function in people with mild to moderate dementia. Although data are conflicting, any real effect is likely to be modest.

Studies show gingko does not seem to alleviate memory loss, tinnitus, or altitude sickness. Gingko may prevent damage to the kidneys caused by the immunosuppressant cyclosporine.

Adverse effects: Nausea, dyspepsia, headache, dizziness, and heart palpitations may occur. Ginkgo may interact with aspirin, other NSAIDs (see p. 1623), and warfarin and may reduce the efficacy of anticonvulsants.

Ginseng

Ginseng is a family of plants. Dietary supplements are derived from American ginseng (*Panax quinquefolius*) or Asian ginseng. Siberian ginseng is a different genus and does not contain the ingredients believed to be active in the 2 forms used in supplements. Ginseng can be taken as fresh or dried roots, extracts, solutions, capsules, tablets, sodas, and teas or used as cosmetics. Active ingredients in American ginseng are panaxosides (saponin glycosides). Active ingredients in Asian ginseng are ginsenosides (triterpenoid glycosides).

Ginseng products vary considerably in quality because many contain little or no detectable active ingredient. In very few cases, some ginseng products from Asia have been purposefully mixed with mandrake root, which has been used to induce vomiting, or with the drugs phenylbutazone or aminopyrine. These drugs have been removed from the US market because of significant adverse effects.

Claims: Ginseng is said to enhance physical (including sexual) and mental performance and to have adaptogenic effects (ie, to increase energy and resistance to the harmful effects of stress and aging). Other claims include reduction in plasma glucose levels; increases in high density lipoprotein (HDL), Hb, and protein levels; stimulation of the immune system; and anticancer, cardiotonic, endocrine, CNS, and estrogenic effects. Some studies have shown that Asian ginseng may lower plasma glucose and have possible beneficial effects on immune function, but there is no evidence for other health claims. Recent Canadian studies show that a polysaccharide extract of *P. quinquefolius* is useful in helping prevent colds.

Adverse effects: Nervousness and excitability may occur but decrease after the first few days. Ability to concentrate may decrease, and plasma glucose may become abnormally low (causing hypoglycemia). Because ginseng has an estrogen-like effect, women who are pregnant or breastfeeding should not take it, nor should children. Occasionally, there are reports of more serious effects, such as asthma attacks, increased BP, palpitations, and, in postmenopausal women, uterine bleeding. To many people, ginseng tastes unpleasant.

Ginseng can interact with antihyperglycemic drugs, aspirin, other NSAIDs, corticosteroids, digoxin, estrogens, monoamine oxidase inhibitors, and warfarin.

Glucosamine

Glucosamine is a precursor of multiple cartilage constituents. It is extracted from chitin (in shells of crabs, oysters, and shrimp) and is taken in tablet or capsule form, usually as glucosamine sulfate, but sometimes as glucosamine hydrochloride. Glucosamine is often taken with chondroitin sulfate (see p. 3425).

Claims: Strong scientific evidence supports use of glucosamine sulfate for treatment of mild to moderate osteoarthritis of the knee. Its role in the treatment of more severe knee osteoarthritis and osteoarthritis in other locations is less well-defined. Some evidence suggests it has both analgesic and disease-modifying effects, whereas evidence from other large and well-designed studies shows it to be of no benefit. One very large study showed that glucosamine hydrochloride is beneficial only when combined with chondroitin sulfate. Mechanism is unknown but may be related to improved glycosaminoglycan synthesis as a result of the sulfate moiety. Dose is 500 mg po tid.

Adverse effects: Allergy (in patients who have shellfish allergy and take forms extracted from shellfish), dyspepsia, fatigue, insomnia, headache, photosensitivity, and nail changes may occur.

Goldenseal

Goldenseal, an endangered US plant, is related to the buttercup. Its active components are hydrastine and berberine, which have antiseptic activity. Berberine also has antidiarrheal properties.

Claims: Goldenseal is used as an antiseptic wash for mouth sores, inflamed and sore eyes, and irritated skin and as a douche for vaginal infections. It has been combined with echinacea as a cold remedy, but the efficacy of goldenseal as a cold remedy has not been proved. Goldenseal is also used as a remedy

for indigestion and diarrhea. In 2 relatively well-designed studies, berberine isolated from goldenseal reduced diarrhea.

Adverse effects: Goldenseal can have many adverse effects, including nausea, anxiety, dyspepsia, uterine contractions, jaundice in neonates, and worsening of hypertension. If taken in large amounts, goldenseal can cause seizures and respiratory failure and may affect contraction of the heart. Goldenseal may interact with warfarin. Women who are pregnant or breastfeeding, neonates, and people who have seizure disorders or problems with blood clotting should not take goldenseal. Berberine may reduce the anticoagulant effect of heparin.

Green Tea

Green tea is made from the dried leaves of the same plant as traditional tea, an evergreen shrub native to Asia. However, traditional tea leaves are fermented, and green tea leaves are steamed but unfermented. Green tea may be brewed and drunk or ingested in extracted tablet or capsule form. It has multiple components that are thought to have antioxidant and anticancer effects. Green tea contains polyphenols and catechins as well as caffeine, but many extracts have been decaffeinated.

Claims: Green tea is said to have multiple health benefits, none of which are supported by strong scientific evidence. It has been used for cancer prevention, weight loss, serum lipid reduction, prevention of coronary artery disease, memory enhancement, relief of osteoarthritis pain, treatment of menopausal symptoms, and longevity.

Adverse effects: Adverse effects are related to effects of caffeine. They include insomnia, anxiety, tachycardia, and mild tremor. Pregnant women should avoid excessive caffeine.

Kava

Kava comes from the root of a shrub (*Piper methysticum*) that grows in the South Pacific. It is ingested as a tea or in capsule form. Active ingredients are thought to be kavalactones.

Claims: Strong scientific evidence supports use of kava as an anxiolytic and sleep aid. Mechanism is unknown. Some people use kava for asthma, menopausal symptoms, and UTIs. Dose is 100 mg of standardized extract tid.

Adverse effects: Over 20 people in Europe developed liver toxicity (including liver failure) after taking kava, which prompted the FDA to mandate a warning label on kava products. Safety is under continuing surveillance.

When kava is prepared traditionally (as tea) and used in high doses (> 6 to 12 g/day of dried root) or over long periods (up to 6 wk), there have been reports of scaly skin rash (kava dermopathy), blood changes (eg, macrocytosis, leukopenia), and neurologic changes (eg, torticollis, oculogyric crisis, worsening of Parkinson's disease, movement disorders). Also, kava may prolong the effect of other sedatives (eg, barbiturates) and affect driving or other activities requiring alertness.

Licorice

Natural licorice, which has a very sweet taste, is extracted from the root of a shrub and used medicinally as a capsule, tablet, or liquid extract. Most licorice candy made in the US is flavored artificially and does not contain natural licorice. Glycyrrhizin is the active ingredient in natural licorice. For people who are particularly sensitive to the effects of glycyrrhizin, specially treated licorice products that contain a much lower amount of glycyrrhizin (about one tenth) are available. These products are called deglycyrrhizinated licorice.

Claims: People most often take licorice to suppress coughs, to soothe a sore throat, and to relieve stomach upset. Applied externally, it is said to soothe skin irritation (eg, eczema). There are not enough data to determine whether licorice is effective for stomach ulcers or complications caused by hepatitis C.

Adverse effects: High doses of real licorice (> 1 oz/day) and glycyrrhizin cause renal Na and water retention, possibly leading to high BP, and K excretion, possibly causing low K levels. Increased K excretion can be a particular problem for people who have heart disease and for those who take digoxin or diuretics that also increase K excretion. Such people and those who have high BP should avoid taking licorice.

Licorice may increase the risk of premature delivery; thus, pregnant women should avoid licorice.

Melatonin

Melatonin, a hormone produced by the pineal gland, regulates circadian rhythms. It is derived from animals or can be manufactured synthetically. In some countries, melatonin is considered a drug and is regulated as such.

Claims: Some scientific evidence supports use of melatonin to minimize the effects of jet lag, especially in people traveling eastward over 2 to 5 time zones. However, in one large well-designed study, melatonin supplements did not relieve symptoms of jet lag, and only a few small studies suggest that these supplements can treat insomnia.

Standard dosage is not established and ranges from 0.5 to 5 mg po taken 1 h before usual bedtime on the day of travel and 2 to 4 nights after arrival. Evidence supporting use of melatonin as a sleep aid in adults and children with neuropsychiatric disorders (eg, pervasive developmental disorders) is less strong.

Adverse effects: Hangover drowsiness, headache, and transient depression may occur. Melatonin may worsen depression. Theoretically, prion infection caused by products derived from neurologic tissues of animals is a risk.

Milk Thistle

Milk thistle is a purple-flowered plant. Its sap and seeds contain the active ingredient silymarin, a potent antioxidant.

Claims: Milk thistle is said to treat cirrhosis and to protect the liver from viral hepatitis, the damaging effects of alcohol, and hepatotoxic drugs. In vitro, silymarin increases levels of intrahepatic glutathione, an antioxidant important for detoxification. Well-designed studies do not show that milk thistle significantly benefits people with liver disease, although individual case reports claim fatality reduction in mushroom poisoning.

Adverse effects: No serious adverse effects have been reported. Milk thistle may intensify the effects of antihyperglycemic drugs and may interfere with indinavir therapy. Women who have hormone-sensitive conditions (eg, breast, uterine, and ovarian cancer; endometriosis; and uterine fibroids) should avoid the above-ground parts of milk thistle.

S-Adenosyl-L-Methionine

S-adenosyl-L-methionine (SAMe) is a derivative of methionine and a cofactor for multiple synthetic pathways. It is produced naturally in the body and is manufactured synthetically in supplement form.

Claims: SAMe is said to be effective for treatment of depression, osteoarthritis, and liver disorders, but scientific studies so far do not confirm this claim. More research is needed to verify its efficacy. It is a platelet inhibitor in vitro.

Adverse effects: No serious adverse effects have been reported. SAMe is contraindicated in patients with bipolar disorder because SAMe can precipitate manic episodes.

Saw Palmetto

Saw palmetto berries contain the plant's active ingredients. The active ingredients, thought to be fatty acids, are unidentified but seem to inhibit 5α-reductase, thus opposing the conversion of testosterone to dihydrotestosterone. The berries can be used to make a tea, or they can be extracted into tablets, capsules, or a liquid preparation. Most formulations evaluated in clinical studies are hexane extracts of saw palmetto berries, which are 80 to 90% essential fatty acids and phytosterols.

Claims: Strong scientific evidence supports use of saw palmetto to treat symptoms of benign prostatic hyperplasia (eg, frequent urination); no evidence suggests it reverses the hyperplasia. Also, one large, well-designed study did not show any benefit.

Claims that it increases sperm production, breast size, or sexual vigor are unproved. Dose is 320 mg once/day or 160 mg bid.

Adverse effects: Headache and diarrhea may occur, but no other serious adverse effects have been reported. Saw palmetto may interact with estrogens; thus, women who are pregnant or who may become pregnant should not take it.

St. John's Wort

The flowers of St. John's wort contain its biologically active ingredients hypericin and hyperforin. St. John's wort may increase CNS serotonin and, in very high doses, acts like a monoamine oxidase inhibitor (MAOI).

Claims: Study findings are variable, but St. John's wort may benefit patients with mild to moderate depression who have no suicidal ideation. A large, well-designed study found it ineffective in treating major depression.

Dose is 300 to 600 mg po once/day of a preparation standardized to 0.2 to 0.3% hypericin, to 1 to 4% hyperforin, or to both (usually). St. John's wort is also said to be useful for treating HIV infection but has proven adverse interactions with protease inhibitors and nonnucleoside reverse transcriptase inhibitors (NNRTIs). A small trial showed St. John's wort (standardized to hypericin but not hyperforin) did not relieve symptoms of attention-deficit/hyperactivity disorder in children.

Adverse effects: Photosensitivity, dry mouth, constipation, dizziness, confusion, and mania (in patients with bipolar disorder) may occur. St. John's wort is contraindicated in pregnant women. Potential adverse interactions occur with cyclosporine, digoxin, iron supplements, MAOIs, NNRTIs, oral contraceptives, protease inhibitors, SSRIs, tricyclic antidepressants, and warfarin.

Valerian

Valerian's root and rhizomes (underground stems) contain its active ingredients, including valepotriates and pungent odiferous oils.

Claims: Valerian is used as a sedative and sleep aid and is especially popular in Europe. In 2 relatively well-designed studies, valerian improved sleep quality and shortened the time needed to fall asleep. However, there is still insufficient clinical data to confirm whether valerian is effective for insomnia.

Some people take valerian for headaches, depression, irregular heartbeat, and trembling. There is not enough scientific evidence to determine whether valerian works for these conditions. It is usually used for short periods of time (4 to 6 wk), and studies suggest that it is generally safe to do so.

Adverse effects: Valerian may prolong the effect of other sedatives (eg, barbiturates) and affect driving or other activities requiring alertness.

Zinc

Zinc, a mineral, is required in small quantities for multiple metabolic processes. Dietary sources include oysters, beef, and fortified cereals.

Claims: Some experts believe that when taken soon after cold symptoms develop, zinc taken as zinc gluconate or acetate lozenges can shorten the course of the common cold. Scientific studies are inconsistent, but if zinc has an effect, it probably is small and occurs only when it is taken very soon after cold symptoms develop.

There is stronger evidence that in developing countries, supplements containing zinc 20 mg and iron taken once/wk reduce mortality in infants who have diarrhea and respiratory infection. There is also strong evidence that supplements containing zinc 80 mg and antioxidants taken once/day slow progression of moderate to severe atrophic (dry form) age-related maculopathy in elderly people.

Adverse effects: Zinc is generally safe, but toxicity can develop if high doses are used (see p. 55). Common adverse effects of zinc lozenges include nausea, vomiting, diarrhea, mouth irritation, mouth sores, and bad taste. Because zinc is a trace metal and can remove other necessary metals from the body, zinc lozenges should not be taken for more than 14 days. Zinc sprays may cause nose and throat irritation. The effects of certain antibiotics may be lowered by the consumption of zinc supplements.

Chapter 346. Smoking Cessation

Introduction

Nicotine is a highly addictive drug present in tobacco and is a major component of cigarette smoke. This drug stimulates the brain reward system activated during pleasurable activities in a manner similar to that of most other addictive drugs (see p. 1507). People smoke to feed their nicotine addiction but simultaneously inhale thousands of other components, including carcinogens, noxious gases, and chemical additives that are a part of cigarette smoke. These toxic components, rather than nicotine, are responsible for the multiple health consequences of smoking.

Epidemiology

Smoking: The percentage of people in the US who smoke cigarettes has declined since 1964, when the Surgeon General first publicized the link between smoking and ill health. Nevertheless, about 20% of adults still smoke. Smoking is most prevalent among men, people with less than a high school education, people living at or below the poverty income level, people with psychiatric disorders (including alcohol and substance use), American Indians, and Alaska natives. Smoking is less common among Hispanics and least common among Asian Americans.

Most smokers start during childhood. Children as young as 10 yr experiment with cigarettes. About 31% become addicted before age 16 and over half before age 18, and age of initiation continues to decrease. The younger the age at which smoking starts, the more likely smoking is to continue. Risk factors for childhood initiation include

- Parental, peer, and role model (eg, celebrity) smoking
- Poor school performance
- A poor relationship with parents or a single-parent home
- High-risk behavior (eg, excessive dieting, particularly among girls; physical fighting and drunk driving, particularly among boys)
- Availability of cigarettes
- Poor problem-solving abilities

Complications: Smoking harms nearly every organ in the body and is the leading cause of preventable mortality in the US, accounting for an estimated 435,000 deaths/yr, or about 20% of all deaths. About half of all current smokers die prematurely of a disease directly caused by smoking, losing 10 to 14 yr of life (7 min/cigarette) on average. Most (65%) smoking-attributable deaths are caused by ischemic heart disease, lung cancer, and chronic lung disease; the rest are caused by noncardiac vascular diseases (eg, stroke, aortic aneurysm), other cancers (eg, bladder, cervical, esophageal, kidney, laryngeal, oropharyngeal, pancreatic, stomach, throat), pneumonia, and perinatal conditions (eg, preterm birth, low birth weight, SIDS). In addition, smoking is a risk factor for other conditions that convey significant morbidity and disability, such as acute myelocytic leukemia, frequent URIs, cataracts, reproductive effects (eg, infertility, spontaneous abortion, ectopic pregnancy, premature menopause), peptic ulcer disease, osteoporosis, and periodontitis.

Quitting: About 70% of US smokers say they want to quit and have already tried to quit at least once. More than 70% of smokers present in a primary care setting every year; yet only a minority receive counseling and drugs to help them quit. Most smokers < 18 yr believe they will not be smoking in 5 yr, and 40 to 50% report having tried to quit in the previous year. However, longitudinal studies show that 73% of daily smokers in high school remain daily smokers 5 to 6 yr later.

Passive smoking: Passive exposure to cigarette smoke (secondhand smoke, environmental tobacco smoke) has grave health implications for children and adults. Risks to neonates, infants, and children

include low birth weight, SIDS, asthma and related respiratory illnesses, and otitis media. Children exposed to cigarette smoke lose more school days because of illness than nonexposed children. Smoking-related fires kill 80 children each year and injure almost 300 more; such fires are the leading cause of deaths resulting from unintentional fires in the US. Treating children for smoking-related illnesses is estimated to cost $4.6 billion/yr. In addition, each year, 43,000 children lose one or more caregivers who die from smoking-related diseases.

For adults, passive exposure is linked to the same neoplastic, respiratory, and cardiovascular diseases that threaten active smokers. Overall, secondhand smoke is estimated to be responsible for 50,000 to 60,000 deaths each year in the US (between 2% and 3% of all deaths). These findings have led states and municipalities across the US to ban smoking within workplaces in an effort to protect the health of workers and others from the substantive risks of environmental tobacco smoke. Currently, > 50% of the US population live in a state that has implemented a comprehensive indoor smoke-free ordinance.

Symptoms and Signs

Smoking cessation often causes intense withdrawal symptoms, primarily a craving for cigarettes but also anxiety, depression (mostly mild, sometimes major), inability to concentrate, irritability, restlessness, insomnia, drowsiness, impatience, hunger, tremor, sweating, dizziness, headaches, and digestive disturbances. These symptoms are worst in the first week (when most smokers trying to quit relapse) and subside within 3 to 4 wk in most patients but may continue for months. An average weight gain of 4 to 5 kg is common and is another reason for recidivism. Coughing and oral ulcers may develop temporarily after quitting. Smokers with ulcerative colitis often experience an exacerbation soon after quitting.

Treatment

• Cessation counseling

• Drug treatment (varenicline, bupropion, or a nicotine replacement product) when not contraindicated

Evidence-based counseling and drug treatment are both effective treatments for tobacco dependence; combining counseling and drug treatment is more effective than either intervention alone.

The addiction and withdrawal symptoms are often powerful enough that even with knowledge of the many health risks, many smokers are unwilling to try quitting, and those attempting to quit are often unsuccessful. Only a minority of smokers achieve long-term remission after their initial attempts to quit; many continue to smoke for many years, cycling through multiple periods of relapse and remission. Overall, counseling, drug treatment, or both can boost success rates up to 4 times that achieved by smokers who try to quit on their own (cold turkey) without these treatments.

Smoking has many characteristics of a chronic disorder. Thus, the optimal evidence-based approach to patients, particularly those unwilling to quit or those who have not yet considered quitting, should be guided by the same principles that guide chronic disease management, namely

• Continually assessing and monitoring smoking status

• Using different evidence-based interventions (or combinations) for different patients and building on their prior experiences and treatment preferences

• Although emphasizing that abstinence is the essential goal, encouraging temporary abstinence and reduction in consumption for patients who fall short of total smoking cessation

Although reduction in consumption can increase motivation to quit (particularly when combined with nicotine replacement therapy), smokers should be reminded that reducing the number of cigarettes smoked may not improve health because smokers often inhale more smoke (and thus more toxins) per cigarette to maintain nicotine intake when they reduce the number of cigarettes smoked per day.

Identifying smokers: Effective interventions require first that smokers be consistently identified (eg, by

expanding the vital signs to include smoking status for all patients at every visit).

Evidence-based counseling: Counseling efforts begin with the 5 A's:

• Ask at every visit whether a patient smokes and document the response.

• Advise all smokers to quit in clear, strong, personalized language they will understand.

• Assess a smoker's willingness to try quitting within the next 30 days.

• Assist those willing to make a quit attempt by providing brief counseling and drugs.

• Arrange a follow-up, preferably within the first week of the quit date.

For smokers willing to quit, clinicians should establish a quit date, preferably within 2 wk, and stress that total abstinence is better than reduction. Past quitting experiences can be reviewed to identify what helped and what did not, and smoking triggers or challenges to quitting should be planned for in advance. For example, alcohol use is associated with relapse, so alcohol restriction or abstinence should be discussed. In addition, quitting is more difficult with another smoker in the household; spouses and housemates can be encouraged to quit together. In general, smokers should be instructed to develop social support among family and friends for their quit attempt, and clinicians should reinforce their availability and assistance in support of the attempt.

In addition to the brief counseling provided by the patient's clinician, in-person counseling programs can help. They usually use cognitive-behavioral techniques and are offered by various commercial and voluntary health programs. Success rates are higher than with self-help programs. All states in the US have telephone quit lines that can provide counseling support (and sometimes nicotine replacement therapy) to smokers trying to quit. People can call 1-800-QUIT-NOW (1-800-784-8669) toll-free anywhere in the US.

Drugs: Effective and safe drugs for smoking cessation include varenicline, bupropion SR, and 5 types of nicotine replacement therapy (in the form of gum, lozenge, patch, inhaler, and nasal spray—see Table 346-1). Bupropion's mechanism may be to increase the brain's release of norepinephrine and dopamine. Varenicline works at the nicotinic acetylcholine receptor (the α-4β-2 subunit), where it acts as a partial agonist, having some nicotinic effects, and as a partial antagonist, blocking the effects of nicotine. Some evidence suggests varenicline is the most effective monotherapy available for smoking cessation.

All 7 recommended drugs for smoking cessation are effective as monotherapies, but new research suggests that combination therapy is even more effective; for example, combining the nicotine patch with a shorter-acting nicotine drug (eg, lozenge, gum, nasal spray, inhaler), bupropion, or both is more effective than monotherapy. When used in combination, the patch helps maintain continuous levels, and use of gum, lozenge, inhaler, or nasal spray enables the patient to rapidly increase nicotine levels in response to immediate cravings. In addition, the combination of bupropion with nicotine products may be more effective than any one therapy alone, particularly the combination of bupropion with a nicotine patch and a short-acting nicotine drug.

Smokers may worry that they may remain dependent on nicotine after using nicotine products for smoking cessation; however, such dependence rarely persists. Drug choice is guided by the clinician's familiarity with the drug, patient preference and previous experience (positive or negative), and contraindications.

Despite their proven efficacy, smoking cessation drugs are used by < 25% of smokers attempting to quit. Reasons include low rates of insurance coverage, clinician concerns about the safety of simultaneous smoking and nicotine replacement, and discouragement because of past unsuccessful quit attempts.

Therapies under investigation for smoking cessation include a vaccine that causes nicotine to be intercepted before the nicotine reaches the brain and the drugs selegiline, bromocriptine, and topiramate.

Drug safety: Contraindications to bupropion include a history of seizures, an eating disorder, and

monoamine oxidase inhibitor use within 2 wk.

Whether bupropion and varenicline increase risk of suicide is not clear. Varenicline and bupropion may increase risk of serious neuropsychiatric effects and accidents. In 2009, the FDA released a boxed warning for both drugs regarding these possible adverse effects. However, most experts recommend varenicline for most smokers because risks of smoking substantially exceed any possible risks of taking the drug. But varenicline should be avoided in smokers with suicidal risk, unstable psychiatric disorders, and possibly major depression.

Nicotine replacement should be used cautiously in patients with certain cardiovascular risks (those within 2 wk of an MI, with serious arrhythmias, or with serious angina); however, most data suggest that such use is safe. Nicotine gum is contraindicated in patients with temporomandibular joint syndrome, and nicotine patches are contraindicated in patients with severe topical sensitization.

Because of safety concerns, inadequate efficacy data, or both, drugs are not recommended for the following:

• Pregnant smokers

• Light smokers (< 10 cigarettes/day)

[Table 346-1. Drugs for Smoking Cessation]

• Adolescents (< age 18)

• Users of smokeless tobacco

Cessation in children: The counseling approach for children is similar to that for adults; however, drugs are not recommended for patients under the age of 18.

Children should be screened for smoking and risk factors by age 10. Parents should be advised to maintain smoke-free households and to communicate the expectation to their children that the children will remain nonsmokers.

For children who smoke, cognitive-behavioral therapy that involves establishing awareness of tobacco use, providing motivations to quit, preparing to quit, and providing strategies to maintain abstinence after cessation are effective in treating nicotine-dependent patients. Alternative approaches to smoking cessation, such as hypnosis and acupuncture, have not proved to be effective and cannot be recommended for routine use.

Prognosis

About 20 million smokers in the US try to quit each year (almost half of all smokers), usually by using a cold turkey or other nonevidence-based approach, resulting in relapse within days, weeks, or months and a long-term success rate of about 5%. In contrast, success rates of up to 20 to 30% are achieved among smokers who use evidence-based cessation counseling and recommended drugs.

Other Kinds of Tobacco

Cigarette smoking is the most harmful form of tobacco use. However, all tobacco products contain toxins and possible carcinogens and even smokeless tobacco products are not safe alternatives to smoking.

Exclusive pipe smoking is relatively rare in the US (< 1% of people ≥ 12 yr), although it has increased among middle and high school students since 1999. In 2008, about 5.3% of people > 12 yr smoked cigars; this percentage has declined since 2000, people < 18 yr comprise the largest group of new cigar smokers. Risks of pipe and cigar smoking include cardiovascular disease; COPD; cancers of the oral cavity, lung, larynx, esophagus, colon, and pancreas; and periodontal disease and tooth loss.

About 3.3% of people ≥ 18 yr and about 7.9% of high school students use smokeless tobacco (chewing tobacco and snuff). Toxicity of smokeless tobacco varies by brand. Risks include cardiovascular disease, oral disorders (eg, cancers, gum recession, gingivitis, periodontitis and its consequences), and teratogenicity.

Cessation: Cessation counseling for smokeless tobacco users, as for cigarette smokers, has been shown to be effective. However, drugs have not proved effective among smokeless tobacco users.

Effectiveness of cessation treatments for pipe and cigar smokers is not well documented. Also, cessation may be affected by whether cigarettes are smoked concurrently and whether smokers inhale.

Chapter 347. Medical Aspects of Travel

Introduction

Planning and preparation reduce medical risks of travel. Travelers should carry their drugs, extra eyeglasses or other corrective lenses (as well as a current written prescription for either), and hearing-aid batteries in a carry-on bag in case their checked baggage is delayed, lost, or stolen. Drugs should be kept in their original labeled containers. Travelers who need to carry opioids, syringes, or large amounts of drugs should have a prescription or verifying letter from a physician to avoid possible security or customs complications. A medical record summary (including ECG for those with significant cardiac history) is invaluable if a traveler becomes ill. Travelers subject to disabling illness (eg, epilepsy) or those with chronic disease should wear a medical identification bracelet or necklace.

Air Travel

Air travel can cause or worsen certain medical problems; some are considered a contraindication to flight (see Table 347-1), and others may cause discomfort. Serious complications are rare.

During a flight, any health care practitioner among the passengers may be asked to help fellow passengers who become ill. Additionally, most commercial aircrafts carry first-aid equipment, including an automatic external cardioverter defibrillator and limited medical supplies. Airline personnel are receiving more first-aid training now than in the past. Although physicians aiding ill or injured passengers are usually protected from litigation by the Good Samaritan concept, they should avoid practicing beyond their training or expertise.

Further information about air travel may be obtained from the medical department of major airlines, the Federal Aviation Administration (www.faa.gov), online travel information sources, or local travel clinics.

Barometric pressure changes: Commercial airplanes and jet aircraft are pressurized only to the equivalent of an altitude of 6000 to 8000 ft (1830 to 2440 m), not to sea level pressure. Thus, air in body cavities or other closed spaces expands by about 25%; this expansion may aggravate certain medical conditions.

Untreated dental problems or recent dental procedures may become painful when air pressure changes. People with upper respiratory inflammation or allergic rhinitis may develop obstructed eustachian tubes, which may cause barotitis media, or obstructed sinus ostia, which may cause barosinusitis. Frequent yawning or closed-nose swallowing during descent, use of decongestant nasal

[**Table 347-1.** Contraindications to Flying]

sprays, or use of antihistamines before or during flight often prevents or relieves these conditions. Some people suck on hard candies during descent.

Air travel is contraindicated for patients who have or are likely to develop pneumothorax (eg, those who have large pulmonary blebs or cavities) and for those in whom air or gas is trapped (eg, those who have an incarcerated bowel, those traveling < 10 days after chest or abdominal surgery, those who have intraocular gas injection) because even modest expansion may cause pain or tissue damage.

Water should be substituted for air in devices secured by air-filled cuffs or balloons (eg, feeding tubes, urinary catheters). Patients with a colostomy should wear a large bag and expect frequent filling due to expansion of intestinal gas.

Children: Children are particularly susceptible to barotitis media and should be given fluids or food during descent to encourage swallowing, which can equalize pressures. Infants can be breastfed or given a bottle or pacifier. Precautions for children with chronic disease (eg, congenital heart disease, chronic lung disease, anemia) are the same as those for adults.

Circadian dysrhythmia (jet lag): Rapid travel across multiple time zones disrupts the normal circadian rhythm (see also p. 1710). Bright sunlight resets the internal clock. Exposure to bright late-afternoon or evening light delays the onset of normal sleep time, and exposure to early-morning light advances the biologic clock, so that sleep time is earlier than usual. Thus, managing exposure to light can help adaptation, particularly on the days after arrival in a new time zone. For example, people traveling westward could maximize exposure to bright afternoon light to help delay sleep time. People traveling eastward could maximize exposure to bright light in the early morning to help awakening and promote earlier sleep.

Short-acting hypnotics (see Table 177-6 on p. 1709) may help people fall asleep at the appropriate local time after eastward travel. However, hypnotics may have adverse effects, such as daytime drowsiness, amnesia, and nighttime insomnia. Long-acting hypnotics increase the likelihood of confusion and falls among the elderly and should be avoided. Melatonin, a hormone secreted by the pineal gland, may provide a time-of-night cue; however, large placebo-controlled trials showing melatonin's safety and efficacy are lacking (see p. 3430). Taking melatonin (0.5 to 5 mg po before the desired sleep time) may help those who need to go to sleep earlier because they have traveled east across several time zones. Some therapeutic regimens must be altered to compensate for circadian dysrhythmia. For example, insulin dosage and timing may require modification depending on the number of time zones traversed, time spent at destination, available food, and activity; glucose must be monitored frequently. Target plasma glucose levels should be increased; because so many changes affect levels, tight control is more difficult, and the risk of hypoglycemia is increased. Regimens may require modification based on elapsed rather than local time.

Decreased O_2 tension: In passenger jets at cruising altitude, with a typical 8000 ft (2440 m) cabin altitude, the partial pressure of O_2 is about 25% less than at sea level, which, because of the O_2-Hb dissociation curve, represents a drop in arterial O_2 saturation of only about 4.4%. This decrease may be significant for people with severe heart or lung disease (see Table 347-1) but is harmless to most people; however, after 3 to 9 h at that altitude equivalent, some people report discomfort (eg, headache, malaise).

In general, anyone who can walk 50 m or climb one flight of stairs and whose disease is stable can tolerate normal passenger jet cabin conditions without additional O_2. However, problems may arise for travelers with moderate or severe pulmonary disease (eg, asthma, COPD, cystic fibrosis), heart failure, anemia with Hb < 8.5 g/dL, severe angina pectoris, sickle cell disease (but not trait), and some congenital heart diseases. When flying is essential, such patients can usually fly safely with specially designed continuous O_2 equipment, which must be provided by the airline. Mild ankle edema due to venous stasis commonly develops during long flights and should not be confused with heart failure.

Smoking can aggravate mild hypoxia and should be avoided before flying. Hypoxia and fatigue may increase the effects of alcohol.

Low cabin humidity: Dehydration may develop because of very low cabin humidity. It can be avoided with adequate fluid intake and alcohol avoidance. Contact lens wearers and people with dry eyes should instill artificial tears frequently to avoid corneal irritation resulting from low cabin humidity.

Motion sickness: Motion sickness is often triggered by turbulence and vibration and is made worse by warmth, anxiety, hunger, or overeating (see also p. 3278). Symptoms may include nausea, vomiting, sweating, and vertigo.

Motion sickness can be minimized before and during travel by moderating intake of food, fluids, and alcohol. Fixing the eyes on a stationary object or on the horizon can help, as can lying down and keeping the eyes closed. Other measures include choosing a seat where motion is felt least (eg, in the center of an airplane, over the wing), refraining from reading, and using an air vent. A scopolamine patch or an OTC or prescription antihistamine is often useful, especially if taken before travel. However, these drugs can cause drowsiness, dry mouth, confusion, falls, and other problems in the elderly.

Pregnancy: Uncomplicated pregnancy through 36 wk is not a contraindication to air travel; high-risk pregnancies must be individually evaluated. Flight during the 9th mo usually requires a physician's written

approval dated within 72 h of departure and indicating expected delivery date. However, policies may vary by airline. Seat belts should be worn below the abdomen, across the hips.

To prevent effects on development of the fetal thyroid, pregnant women should avoid prolonged use of water purification tablets that contain iodine. If possible, pregnant women should avoid travel to areas where malaria is endemic because malaria can be more virulent in pregnant women, and the safety of all antimalarial prophylactic drugs during pregnancy has not been fully studied. When traveling, pregnant women should be particularly careful about following safe food guidelines and hand washing.

Psychologic stress: Hypnosis and behavior modification benefit some people with fear of flying or claustrophobia. Fearful passengers may also benefit from a short-acting anxiolytic (eg, zolpidem, alprazolam) taken before and, depending on duration, during flight. Hyperventilation commonly simulates heart disease and may cause tetany-like symptoms; anxiety and hyperventilation can cause panic, paranoia, and a sense of impending death. Psychotic tendencies may become more acute and troublesome during flight. Patients with violent or unpredictable tendencies must be accompanied by an attendant and appropriately sedated.

Restricted mobility: Deep venous thrombosis may develop in anyone sitting for long periods and may result in a pulmonary embolus. Risk factors include those for non-altitude-related deep venous thrombosis (eg, prior deep venous thrombosis, pregnancy, use of oral contraceptives). Frequent (every 1 to 2 h) ambulation, short-movement exercises while seated, and adequate hydration are recommended; however, studies showing benefit from these measures are lacking.

Turbulence: Turbulence may cause motion sickness or injury. While seated, passengers should keep their seat belts fastened at all times.

Other issues: Most implanted cardiac devices, including pacemakers and cardioverter defibrillators, are effectively shielded from interference from security devices. However, the metal content of some of these devices, as well as certain orthopedic prostheses and braces, may trigger a security alarm. A physician's letter should be carried to avoid security difficulties.

People with specific dietary and medical needs should plan carefully and carry their own food and supplies. With several days' notice, all airlines departing from or arriving in the US (and most others) can make reasonable efforts to accommodate passengers with physical handicaps and special needs, including those who require O_2 therapy. Wheelchairs can be accommodated on all US airlines and most foreign ones, but advance notice is advisable. Some airlines accept passengers requiring more highly specialized equipment (eg, IV fluids, respirators) provided that appropriate personnel accompany the passenger and arrangements have been made in advance. If travelers cannot be accommodated on a commercial aircraft because of severe illness, air ambulance service is necessary.

Foreign Travel

About 1 in 30 people traveling abroad requires emergency care. Illness in a foreign country may involve significant difficulties. Many insurance plans, including Medicare, are not valid in foreign countries; overseas hospitals often require a substantial cash deposit for nonresidents, regardless of insurance. Travel insurance plans, including some that arrange for emergency evacuation, are available through commercial insurance agents, travel agencies, and some major credit card companies. Directories listing English-speaking physicians in foreign countries, US consulates who may assist in obtaining emergency medical services, and information about foreign travel risks are available (see Table 347-2). Patients with serious disorders should consider pretravel contact or arrangements with an organization that offers medically supervised evacuation from foreign countries. Certain infections are common when traveling to certain areas.

Vaccinations: Some countries require specific vaccinations (see Table 347-3). General

[**Table 347-2.** Useful Contacts for People Traveling Abroad]

travel and up-to-date immunization information and malaria chemoprophylaxis requirements are available from the Centers for Disease Control and Prevention (CDC) malaria hotline and web site (see also the CDC recommendations, Travelers' Health: Vaccinations and Malaria: Malaria and Travelers).

Injury and death: Road traffic accidents are the most frequent cause of death of nonelderly international travelers. Travelers should use seat belts in vehicles and a helmet when cycling. Travelers should avoid motorcycles and mopeds and avoid riding on bus roofs or in open truck beds. To prevent drowning (another common cause of death while abroad), travelers should avoid beaches with turbulent surf and avoid swimming after drinking alcoholic beverages.

Traveler's diarrhea: Traveler's diarrhea (TD—see also p. 150) is the most common health problem among international travelers. TD is usually self-limited, typically resolving in 5 days; however, 3 to 10% of travelers with TD may have symptoms lasting > 2 wk, and up to 3% of travelers have TD lasting > 30 days. TD lasting < 1 wk requires no testing. For persistent TD, laboratory testing is done (see p. 90).

Self-initiated treatment is indicated for moderate to severe symptoms (≥ 3 unformed stools over 8 h), especially if vomiting, fever, abdominal cramps, or blood in the stool are present. Treatment is with an appropriate antibiotic (eg, a fluoroquinolone for most destinations, a macrolide such as azithromycin for Southeast Asia). Additional measures include loperamide (except in patients with fever, bloody stools, or abdominal pain and in children < 2 yr); replacement of fluids; and, in the elderly and small children, electrolytes (eg, oral rehydration solution).

Measures that may decrease the risk of TD include

• Drinking and brushing teeth with bottled, filtered, boiled, or chlorinated water

• Avoiding ice

• Eating freshly prepared foods only if they have been heated to steaming temperatures

• Eating only fruits and vegetables that travelers peel or shell themselves

• Avoiding food from street vendors

• Washing hands frequently

• Avoiding all foods likely to have been exposed to flies

Prophylactic antibiotics (eg, fluoroquinolones) are effective in preventing diarrhea, but because of concerns about adverse effects and development of resistance, they should probably be reserved for immunocompromised patients.

Schistosomiasis: Schistosomiasis is common and is caused by exposure to still water in Africa, Southeast Asia, China, and eastern South America. Schistosomiasis can be prevented by wearing footwear and socks when walking through water and by avoiding freshwater activities in areas where schistosomiasis is common (see p. 1358).

Problems after returning home: Persistent TD is the most common medical problem after

[**Table 347-3.** Vaccines for International Travel*,†]

travel. Malaria (see p. 1381), hepatitis A and B (see p. 246), typhoid fever (see p. 1259), sexually transmitted diseases (see p. 1466), including HIV infection (see p. 1438), amebiasis (see p. 1367), and meningitis (see p. 1734) are the most commonly acquired potentially serious diseases. People can also acquire lice (see p. 711) and scabies (see p. 713) after being in crowded living conditions or places where hygienic measures are poor.

Some diseases become evident months after a traveler has returned home; a travel history with exposure risks is a useful diagnostic clue when patients present with a puzzling illness. The International Society of Travel Medicine (www.istm.org) and the American Society of Tropical Medicine and Hygiene (www.astmh.org) have lists of travel clinics on their web sites. Many of these clinics specialize in assisting travelers who are ill after their return home.

Chapter 348. Syndromes of Uncertain Origin

Introduction

Many patients have syndromes for which no specific cause has been identified. Some physicians think that some of these syndromes have psychologic causes, but many physicians and most patients with one of these syndromes reject that idea. Some data—often incomplete, inconsistent, or contradictory—suggest a physical cause, although the exact cause remains uncertain. The causative or contributory role of psychologic factors is also uncertain.

Some patients have scattered, apparently unrelated symptoms that do not form a recognizable syndrome. With better definitions, case recognition may improve; further study of patients with such symptoms is needed to clarify symptom etiology and the clinical significance of these syndromes, to develop appropriate diagnostic strategies, and to define optimum care.

The evaluating physician's first responsibility is to obtain a thorough history, including history of exposure to potentially noxious substances, and to exclude specific, potentially treatable alternative diagnoses. Early stages of known disorders and atypically manifesting common disorders should be considered first. Often, there is little guidance as to what testing is appropriate, but the physician must avoid tests that are inappropriate or not clearly indicated. If no treatable cause is identified after the evaluation, supportive, empathic follow-up is required. A physician should be aware that many patients with such syndromes turn to complementary and alternative medical practices (see p. 3411) in their search for relief.

Chronic Fatigue Syndrome

Chronic fatigue syndrome (CFS) is defined as longstanding, severe, disabling fatigue without demonstrable muscle weakness. Underlying disorders that could explain the fatigue are absent. Depression, anxiety, and other psychologic diagnoses are typically absent. Treatment is psychologic support, often including antidepressants, and limited rest.

This definition of CFS has several variants, and heterogeneity among patients who meet the criteria of this definition is considerable. Prevalence is impossible to state precisely; it is usually estimated to be between 7 and 38/100,000 people. However, a recent telephone survey found the prevalence to be many times higher. Prevalence estimates may vary because of differences in diagnostic evaluation, physician-patient attitudes, social acceptability, risk of exposure to an infectious or toxic agent, or definition and case finding. CFS occurs slightly more often in women. In office-based studies, prevalence is highest among whites. However, community surveys indicate a higher prevalence among blacks, Hispanics, and American Indians than among whites.

Etiology

Etiology is controversial, and the precise cause remains unknown. Psychologic factors may be the cause in an unknown percentage of cases; however, CFS seems to be distinct from typical depression, anxiety, or other psychologic disorders. A chronic viral infection has been proposed as a cause because many patients relate onset of CFS to an acute bout of Lyme disease, mononucleosis, influenza, Q fever, Ross River virus, parvovirus, and other infectious diseases. Epstein-Barr virus has also been proposed as a cause, but immunologic markers of exposure do not appear to be sensitive or specific. Other possible but unproven viral causes include rubella, HIV, enteroviruses, human herpesvirus 6, and human T-cell lymphotropic virus. Allergic reactions have also been proposed; about 65% of patients report previous allergies, and the rate of cutaneous reactivity to inhalants or foods is 25 to 50% higher in this group than in the general population.

Various immunologic abnormalities have been reported. They include low levels of IgG, decreased lymphocytic proliferation, low interferon-γ levels in response to mitogens, and poor cytotoxicity of natural killer cells. Some patients have abnormal IgG, with circulating autoantibodies and immune complexes. Many other immunologic abnormalities have been studied; none provides adequate sensitivity and specificity for defining CFS. Additionally, no consistent or readily reproducible pattern of immunologic abnormalities has been identified.

Other proposed mechanisms include neuroendocrine abnormalities, abnormal levels of neurotransmitters, inadequate cerebral circulation, prolonged bed rest, undernutrition, and elevated levels of ACE.

Data indicate that relatives of patients with CFS have an increased risk of developing the syndrome, suggesting a familial or genetic component.

Some researchers believe the syndrome ultimately will prove to have multiple causes, including genetic predisposition and exposure to microbial agents, toxins, and other physical and emotional traumas.

Symptoms and Signs

Onset is usually abrupt, and many patients report an initial viral-like illness with swollen lymph nodes, extreme fatigue, fever, and upper respiratory symptoms. The main symptom is severe fatigue (usually for ≥ 6 mo) that interferes with daily activities (see Table 348-1 for usual symptoms and signs).

Usually, no signs of muscle weakness, arthritis, neuropathy, or organomegaly are present. However, some definitions require the presence of low-grade fever, nonexudative pharyngitis, or palpable or tender lymph nodes.

Diagnosis

• Clinical criteria

[**Table 348-1.** Diagnostic Criteria for Chronic Fatigue Syndrome]

Because there is no definitive diagnostic test, diagnosis is by clinical criteria (see Table 348-1). However, because multiple definitions exist, the criteria are not agreed on universally and should not always be strictly applied to individual patients. The criteria are more useful for epidemiologic and clinical studies than for excluding the diagnosis in individual patients. Further evaluation aims to exclude treatable disorders. A reasonable assessment includes CBC and measurement of electrolytes, ESR, and thyroid-stimulating hormone. In some cases, chest x-ray and tests for antinuclear antibody, rheumatoid factor, hepatitis, and HIV should be added. Other viral antibody and other expensive tests are unlikely to shed light on the diagnosis or cause. Obvious depression or severe anxiety excludes the diagnosis of CFS.

Treatment

• Sometimes nonsedating antidepressants

• Sometimes psychologic intervention, physical rehabilitation, and/or regular exercise

• Avoidance of prolonged rest

Nonsedating antidepressants are commonly prescribed, although their value is undetermined. Antiviral treatments with acyclovir and amantadine do not seem effective. Valganciclovir is under study. Studies of immunologic treatments, including high-dose immune globulins, dialyzable WBC extract, amphigen, interferons, isoprinosine, and corticosteroids, have been inconclusive and mostly disappointing. Dietary supplements and high-dose vitamins are commonly used, but their usefulness has not been substantiated.

Psychologic intervention (eg, individual or group therapy) may help some patients, as may formal, structured physical rehabilitation programs. Regular aerobic exercise (eg, walking, swimming, cycling, jogging) under close medical supervision may reduce fatigue and improve physical function.

Persistent or prolonged rest should be firmly discouraged because it can worsen deconditioning and promote progressive frailty.

Symptoms tend to lessen over time.

Multiple Chemical Sensitivity Syndrome

(Idiopathic Environmental Intolerance)

Multiple chemical sensitivity syndrome is characterized by recurrent, nonspecific symptoms attributed to low-level exposure to chemically unrelated substances commonly occurring in the environment. Symptoms are numerous, often involving multiple organ systems, but physical findings are unremarkable. Diagnosis is by exclusion. Treatment is psychologic support and avoidance of perceived triggers, although triggers rarely can be defined.

No universally accepted definition exists, but multiple chemical sensitivity syndrome is generally defined as the development of multiple symptoms attributed to exposure to any number of identifiable or unidentifiable chemical substances (inhaled, touched, or ingested) in the absence of clinically detectable organ dysfunction or related physical signs.

Etiology

Triggers: Reported triggers for multiple chemical sensitivity include

• Alcohol and drugs

• Caffeine and food additives

• Carpet and furniture odors

• Fuel odors and engine exhaust

• Painting materials

• Perfume and other scented products

• Pesticides and herbicides

Mechanism: Many theories—immunologic and nonimmunologic—have been proposed. These theories are all hampered by lack of a consistent dose response to proposed causative substances; ie, symptoms may not be replicated after exposure to high levels of a substance that previously, at much lower levels, seemed to provoke a reaction. Similarly, consistent objective evidence of systemic inflammation, cytokine excess, or immune system activation in relation to symptoms is lacking. Many physicians consider the etiology to be psychologic, probably a form of somatization disorder (see p. 1577). Others suggest that the syndrome is a type of panic attack (see p. 1496) or agoraphobia. Some facets of the syndrome resemble the no-longer-used psychologic diagnosis of neurasthenia.

Multiple chemical sensitivity syndrome develops in 40% of people with chronic fatigue syndrome and in 16% of people with fibromyalgia.

Although measurable biologic abnormalities (eg, decreased levels of B cells, elevated levels of IgE) are rare, some patients have such abnormalities. However, these abnormalities appear without a consistent pattern, and their significance is uncertain.

Symptoms and Signs

Symptoms (eg, palpitations, chest pain, sweating, shortness of breath, fatigue, flushing, dizziness, nausea, choking, trembling, numbness, coughing, hoarseness, difficulty concentrating) are numerous and usually involve more than one organ system. Most patients present with a long list of suspected agents, self-identified or identified by a physician during previous testing. Such patients often go to great lengths

to avoid these agents by changing residence and employment, avoiding all foods containing "chemicals," sometimes wearing masks in public, or avoiding public settings altogether. Physical examination is characteristically unremarkable.

Diagnosis

Diagnosis initially involves exclusion of demonstrable allergies and other known disorders with similar manifestation (eg, atopic disorders such as asthma, allergic rhinitis, food allergies, and angioedema). Atopic disorders are excluded based on a typical clinical history, skin-prick testing, serum assays of specific IgE, or all 3. Consultation with an allergy specialist may be necessary. Building-related illnesses, including sick building syndrome, in which many people who spend time in the same building develop symptoms (see p. 1976), should be considered.

Treatment

Despite an uncertain cause-and-effect relationship, treatment is usually aimed at avoiding the suspected precipitating agents, which may be difficult because many are ubiquitous. However, social isolation and costly and highly disruptive avoidance behaviors should be discouraged.

Psychologic evaluation and intervention may help, but characteristically many patients resist this approach. However, the point of this approach is not to show that the cause is psychologic but rather to help patients cope with their symptoms.

Gulf War Syndrome

Gulf War syndrome is a group of symptoms experienced by > 100,000 American, British, and Canadian veterans of the 1991 Persian Gulf War.

Within a few months of returning from the Persian Gulf, veterans from different military units in the US, Britain, and Canada began reporting various unexplained symptoms, including headache, fatigue, difficulty sleeping, joint pain, chest pain, rashes, and diarrhea. In most cases, however, objective evidence of abnormalities was lacking. Even when symptoms such as a rash, could be confirmed, no specific cause could be identified.

The cause of Gulf War syndrome is unknown. Gulf War veterans often have been exposed to a number of potentially toxic substances, including chemical weapons, depleted uranium weapons, insecticides, and smoke from burning oil wells. Veterans may also have been exposed to irritant petroleum products, decontamination solutions, and a variety of airborne substances that may have caused allergies. Vaccination with the anthrax vaccine, which was given to US military personnel involved in the Gulf War as protection against biological warfare, has also been proposed as a cause, although this vaccine has not caused symptoms in other recipients. The use of pyridostigmine tablets to help prevent the lethal effects of chemical weapons has been suggested as a possible cause as well. However, none of these agents has been linked convincingly to Gulf War syndrome; many exposed people have been asymptomatic, and many symptomatic people have had no identifiable exposure.

Symptoms predominantly involve the nervous system. They include problems with memory, reasoning, concentration, and attention; difficulty falling asleep; depression; fatigue; and headache. Other symptoms may include disorientation, dizziness, erectile dysfunction (impotence), myalgias, fatigue, weakness, paresthesias, diarrhea, rashes, cough, and chest pain.

Diagnosis and treatment have not been established; therefore, the aim is to relieve symptoms.

Veterans who have Gulf War syndrome do not have a higher hospitalization or death rate than anyone else of the same age.

Chapter 349. Care of the Surgical Patient

Introduction

Care of surgical patients often involves nonsurgical consultants (eg, primary care physicians, specialists), who may be asked to provide preoperative risk assessment (sometimes requested as medical clearance), suggest ways to minimize perioperative risks (eg, deep venous thrombosis, endocarditis), and manage complex medical conditions. Psychiatric consultation may be needed to assess capacity or help deal with underlying psychiatric problems that can interfere with recovery. Elderly patients may benefit from involvement of an interdisciplinary geriatric team (see p. 3115), which may need to involve social workers, therapists, ethicists, and other practitioners.

Preoperative Evaluation

If an emergency procedure is required, preoperative evaluation must be rapid and is thus limited. In other cases, the surgical team may consult an internist to obtain a formal preoperative evaluation, which helps minimize risk by identifying correctable abnormalities and by determining whether additional monitoring is needed or whether a procedure should be delayed so that an underlying disorder (eg, hypertension, hyperglycemia, hematologic abnormalities) can be controlled optimally.

Routine preoperative evaluation varies substantially from patient to patient, depending on the patient's age, general health, and risks of the procedure.

History: A relevant preoperative history includes information about all of the following:

- Current symptoms suggesting an active cardiopulmonary disorder (eg, cough, chest pain, dyspnea during exertion, ankle swelling) or infection (eg, fever, dysuria)
- Risk factors for thromboembolism (see p. 2224), excessive bleeding (see p. 968), or infection
- Known disorders that increase risk of complications, particularly hypertension, heart disease, kidney disease, liver disease, diabetes, asthma, COPD, and bleeding disorders
- Previous surgery, anesthesia, or both, particularly their complications
- Allergies
- Tobacco and alcohol use
- Current prescription and nonprescription drug and supplement use

If an indwelling catheter may be needed, patients should be asked about prior urinary retention and prostate surgery.

Physical examination: Physical examination should include not only areas affected by the surgical procedure but also the cardiopulmonary system and a search for any signs of ongoing infection (eg, upper respiratory tract, skin). When spinal anesthesia is likely, patients should be evaluated for scoliosis and other anatomic abnormalities that may complicate lumbar puncture. Any cognitive dysfunction, especially in elderly patients who will be given a general anesthetic, should be noted. Preexisting dysfunction may become more apparent postoperatively and, if undetected beforehand, may be misinterpreted as a surgical complication.

Testing: No preoperative tests are required in healthy patients undergoing operations with very low risk of significant bleeding or other complications; abnormal results are more likely to be false positives than in patients with symptoms or risk factors. In symptomatic patients or in patients undergoing operations with a higher risk of significant bleeding or other complications, laboratory evaluation may include the following tests:

- CBC and urinalysis (glucose, protein, and cells) usually are done.
- Serum electrolytes and creatinine and plasma glucose are measured unless patients are extremely healthy and < 50, the procedure is considered very low risk, and use of nephrotoxic drugs is not expected.
- Liver enzymes are measured if abnormalities are suspected based on the patient's history or examination.
- Coagulation studies and bleeding time are needed only if patients have a history of bleeding diathesis or a disorder associated with bleeding.
- ECG is done for patients at risk of coronary artery disease, including all men > 45 and women > 55.
- If a general anesthetic is to be used, a chest x-ray typically is done (or a recent x-ray is reviewed), although its usefulness is limited, particularly in younger patients and in patients without suspicion of heart or lung disease.
- Pulmonary function testing may be done if patients have a known chronic pulmonary disorder or symptoms or signs of pulmonary disease.

Patients with symptomatic coronary artery disease need additional tests (eg, stress testing, coronary angiography) before surgery.

Surgical risk factors: Surgical risk varies with patient risk factors and the procedure.

Procedural risk is highest with the following:

- Heart or lung surgery
- Prostatectomy
- Major orthopedic procedures (eg, hip replacement)

Patients undergoing elective surgery that has a significant risk of hemorrhage should consider autologous transfusion (see p. 1037). Autologous transfusion decreases the risks of infection and transfusion reactions. Emergency surgery also has a higher risk of morbidity and mortality.

Patient risk factors are stratified by some clinicians using published criteria (see Table 349-1). Older age is associated with decreased physiologic reserve and greater morbidity if a complication occurs. However, chronic disorders are more closely associated with increased postoperative morbidity and mortality than is age alone. Older age is not an absolute contraindication to surgery.

Cardiac risk factors dramatically increase surgical risk. Among the most serious are the following:

- Unstable angina
- Recent MI
- Poorly controlled heart failure

When a heart disorder cannot be corrected before surgery, intraoperative and sometimes preoperative monitoring with pulmonary artery catheterization may be advised.

Incidental infections (eg, UTIs) should be treated with antibiotics but should not delay surgery unless prosthetic material is being implanted; in such cases, incidental infections should be controlled or eliminated before surgery if possible.

Fluid and electrolyte imbalance should be corrected before surgery if possible. Dehydration should be treated with IV normal saline because BP tends to fall when anesthesia is induced. K deficiencies should be corrected to reduce risk of arrhythmias.

Undernutrition (see p. 9) increases surgical risk. For example, serum albumin < 2.8 g/dL is associated with increased morbidity and mortality. If surgery can be delayed for several weeks, sometimes nutritional deficiencies are correctable. Usually, the patient's calorie and protein intake should be increased during the perioperative period. Obesity is unlikely to be correctable in the time available.

Perioperative Management

Usually, an anesthesiologist reviews a patient's drugs and stipulates which ones should be taken on the day of surgery. Such a review

[**Table 349-1.** Cardiac Risk Index in Noncardiac Surgery]

is necessary because some drugs interact with general anesthetics.

Diabetes: On the day of surgery, patients with insulin-dependent diabetes are typically given one third of their usual insulin dose in the morning. Those who take oral drugs are given half of their usual dose. If possible, surgery is done early in the day. The anesthesiologist monitors plasma glucose during surgery and gives additional insulin or dextrose as needed. Close monitoring with fingerstick testing continues throughout the perioperative period.

Corticosteroids: Patients who are taking corticosteroids (mineralocorticoids or glucocorticoids) or have taken them within the previous 3 to 6 mo should be given supplemental doses of these drugs in case perioperative stress (eg, fluid shifts, hypotension) causes adrenal suppression.

Anticoagulants and antiplatelets: Anticoagulants (eg, warfarin) and antiplatelet drugs (eg, aspirin) are usually stopped 5 to 7 days before surgery. However, if the procedure has a low risk of bleeding, an anticoagulant may be continued even on the day of the procedure, although the risk of postoperative bleeding slightly increases.

Other drugs that control chronic disorders: Most drugs taken to control chronic disorders, especially cardiovascular drugs (including antihypertensives), should be continued throughout the perioperative period. Most oral drugs can be given with a small sip of water on the day of surgery. Others may have to be given parenterally or delayed until after surgery. Anticonvulsant levels should be measured preoperatively in patients with a seizure disorder.

Drug dependence: Patients who are dependent on drugs or alcohol may experience withdrawal during the perioperative period. Alcoholics should be given prophylactic benzodiazepines (eg, chlordiazepoxide, diazepam, lorazepam) starting at admission. Opioid addicts may be given opioid analgesics to prevent withdrawal; for pain relief, they may require larger doses than patients who are not addicted. Rarely, opioid addicts require methadone to prevent withdrawal during the perioperative period.

Smoking: Smokers are advised to stop smoking as early as possible before any procedure involving the chest or abdomen. Several weeks of smoking cessation are required for ciliary mechanisms to recover. An incentive inspirometer should be used before and after surgery.

Upper airway: Before intubation, dentures must be removed. Ideally, before patients are moved from the preanesthetic holding area, they should give dentures to a family member. Patients with a deviated septum or another airway abnormality should be evaluated by an anesthesiologist before surgery requiring intubation.

Preprocedural checklist: In the operating room, before the procedure begins, a time out is held during which the team confirms several important factors:

- Patient identity
- Correct procedure and operative site (if applicable)
- Availability of all needed equipment
- Completion of indicated prophylaxis (eg, antibiotics, anticoagulants)

Outpatient Procedures

Many surgical procedures are done in outpatient settings. Patients are evaluated (eg, with laboratory tests—see p. 3445) one to several days before the procedure.

Preparation: The general rule is for patients to have no oral intake after midnight the night before surgery. For certain GI procedures, cleansing enemas or oral solutions must be started 1 to 2 days before surgery. When prophylactic antibiotics are needed before a procedure, the initial dose must be given within 1 h before the surgical incision.

Discharge precautions: Before discharge, patients should be free of severe pain and should be able to think clearly, breathe normally, drink, walk, and urinate.

If sedatives (eg, opioids, benzodiazepines) were used during an outpatient procedure, patients should not leave the hospital unaccompanied. Even after anesthetic effects have apparently worn off and patients feel fine, they are likely to be weak and have subtle residual effects that make driving inadvisable; many patients require opioids for pain. Elderly patients may be temporarily disoriented because of the combined effects of anesthesia and surgical stress and may develop urinary retention caused by immobility and anticholinergic drug effects.

Antibiotic Prophylaxis

Most surgical procedures do not require prophylactic or postoperative antibiotics. However, certain patient-related and procedure-related factors alter the risk-benefit ratio in favor of prophylactic use.

Patient-related factors include certain valvular heart disorders and immunosuppression. Procedures with higher risk involve areas where bacterial seeding is likely:

- Mouth
- GI tract
- Respiratory tract
- GU tract

In so-called clean (likely to be sterile) procedures, prophylaxis generally is beneficial only when prosthetic material or devices are being inserted or when the consequence of infection is known to be serious (eg, mediastinitis after coronary artery bypass grafting).

Drug choice is based on the bacteria most likely to contaminate the wound during a specific procedure. For commonly recommended regimens by procedure, see Table 349-2. Prophylaxis requires that the appropriate antibiotic is given within 1 h before the procedure. Antibiotics may be given orally or IV, depending on the procedure. The need for additional doses after the procedure is controversial, but for clean operations, no additional doses are needed. Postoperative antibiotics are continued > 24 h only when an active infection is detected during surgery; antibiotics are then considered treatment, not prophylaxis.

Postoperative Care

Postoperative care begins in the recovery room and continues throughout the recovery period. Critical concerns are airway clearance, pain control, mental status, and wound healing. Other important concerns are preventing urinary retention, constipation, deep venous thrombosis, and BP variability (high or low). For patients with diabetes, plasma glucose levels are monitored closely by fingerstick testing every 1 to 4 h until patients are awake and eating because better glycemic control improves outcome.

Airway: Most patients are extubated before leaving the operating room and soon become able to clear secretions from their airway. Patients should not leave the recovery room until they can clear and protect their airway (unless they are going to an ICU). After intubation, patients with normal lungs and trachea may have a mild cough for 24 h after extubation; for smokers and patients with a history of bronchitis, postextubation coughing lasts longer. Most patients who have been

[**Table 349-2.** Antimicrobial Preoperative Prophylaxis Guidelines]

intubated, especially smokers and patients with a lung disorder, benefit from an incentive inspirometer.

Postoperative dyspnea may be caused by pain secondary to chest or abdominal incisions (nonhypoxic dyspnea) or by hypoxemia (hypoxic dyspnea—see also p. 2250). Hypoxemia secondary to pulmonary dysfunction is usually accompanied by dyspnea, tachypnea, or both; however, oversedation may cause hypoxemia but blunt dyspnea, tachypnea, or both. Thus, sedated patients should be monitored with pulse oximetry or capnometry. Hypoxic dyspnea may result from atelectasis or, especially in patients with a history of heart failure or chronic kidney disease, fluid overload. Whether dyspnea is hypoxic or nonhypoxic must be determined by pulse oximetry and sometimes ABGs; chest x-ray can help differentiate fluid overload from atelectasis.

Hypoxic dyspnea is treated with oxygen. Nonhypoxic dyspnea may be treated with anxiolytics or analgesics.

Pain: Pain control may be necessary as soon as patients are conscious (see p. 1623). Opioids are typically the first-line choice and can be given orally or parenterally. Often, oxycodone/acetaminophen 1 or 2 tablets (each tablet can contain 2.5 to 10 mg oxycodone and 325 to 650 mg acetaminophen) po q 4 to 6 h or morphine 2 to 4 mg IV q 3 h is given as a starting dose, which is subsequently adjusted as needed; individual needs and tolerances can vary several-fold. With less frequent dosing, breakthrough pain, which should be avoided, is possible. For more severe pain, IV patient-controlled, on-demand dosing is best (see p. 1627). If patients do not have a renal disorder or a history of GI bleeding, giving NSAIDs at regular intervals may reduce breakthrough pain, allowing the opioid dosage to be reduced.

Mental status: All patients are briefly confused when they come out of anesthesia. The elderly, especially those with dementia, are at risk of postoperative delirium, which can delay discharge and increase risk of death. Risk of delirium is high when anticholinergics are used. These drugs are sometimes used before or during surgery to decrease upper airway secretions, but they should be avoided whenever possible. Opioids, given postoperatively, may also cause delirium, as can high doses of H_2 blockers. The mental status of elderly patients should be assessed frequently during the postoperative period. If delirium occurs, oxygenation should be assessed, and all nonessential drugs should be stopped. Patients should be mobilized as they are able, and any electrolyte or fluid imbalances should be corrected.

Wound care: The surgeon must individualize care of each wound, but the sterile dressing placed in the operating room is generally left intact for 24 h unless signs of infection (eg, increasing pain, erythema, drainage) develop. After 24 h, the site should be checked twice/day, if possible, for signs of infection. If they occur, wound exploration and drainage of abscesses, systemic antibiotics, or both may be required. Topical antibiotics are usually not helpful. A drain tube, if present, must be monitored for quantity and quality of the fluid collected. Sutures, skin staples, and other closures are usually left in place 7 days or longer depending on the site and the patient. Face and neck wounds may be superficially healed in 3 days; wounds on the lower extremities may take weeks to heal to a similar degree.

Deep venous thrombosis (DVT) prophylaxis: Risk of DVT after surgery is small, but because

consequences can be severe and risk is still higher than that in the general population, prophylaxis is often warranted. Surgery itself increases coagulability and often requires prolonged immobility, another risk factor for DVT (see Chs. 194 and 219). Prophylaxis for DVT usually begins in the operating room (see Table 194-5 on p. 1920). Alternatively, heparin may be started shortly after surgery, when risk of bleeding has decreased. Patients should begin moving their limbs as soon as it is safe for them to do so.

Fever: A common cause of fever is a high metabolic rate that occurs with the stress of an operation. Other causes include pneumonia, UTIs, and wound infections. Incentive spirometry and periodic coughing can help decrease risk of pneumonia.

Other issues: Certain types of surgery require additional precautions. For example, hip surgery requires that patients be moved and positioned so that the hip does not dislocate. Any physician moving such patients for any reason, including auscultating the lungs, must know the positioning protocol to avoid doing harm; often, a nurse is the best instructor.

Urinary retention and constipation are common after surgery. Causes include use of anticholinergics or opioids, immobility, and decreased oral intake. Patients must be monitored for urinary retention. Straight catheterization is typically necessary for patients who have a distended bladder and are uncomfortable or who have not urinated for 6 to 8 h after surgery; Crede's maneuver sometimes helps and may make catheterization unnecessary. Chronic retention is best treated by avoiding causative drugs and by having patients sit up as often as possible. Bethanechol 5 to 10 mg can be tried in patients unlikely to have any bladder obstruction and who have not had a laparotomy; doses can be repeated every hour up to a maximum of 50 mg/day. Sometimes an indwelling bladder catheter is needed, especially if patients have a history of retention or a large initial output after straight catheterization. Constipation is treated by avoiding causative drugs and, if patients have not had GI surgery, by giving stimulant laxatives (eg, bisacodyl, senna, cascara). Stool softeners (eg, docusate) do not alleviate postoperative constipation.

Loss of muscle mass (sarcopenia) and strength occur in all patients who require prolonged bed rest. With complete bed rest, young adults lose about 1% of muscle mass/day, but the elderly lose up to 5%/day because growth hormone levels decrease with aging. Avoiding sarcopenia is essential to recovery. Thus, patients should sit up in bed, transfer to a chair, stand, and exercise as much as and as soon as is safe for their surgical and medical condition. Nutritional deficiencies may also contribute to sarcopenia. Thus, nutritional intake of patients on complete bed rest should be optimized. Tube feeding or, rarely, parenteral feeding may be necessary.

Chapter 350. Rehabilitation

Introduction

Rehabilitation aims to facilitate recovery from loss of function. Loss may be due to fracture, amputation, stroke or another neurologic disorder, arthritis, cardiac impairment, or prolonged deconditioning (eg, after some disorders and surgical procedures). Rehabilitation may involve physical, occupational, and speech therapy; psychologic counseling; and social services. For some patients, the goal is complete recovery with full, unrestricted function; for others, it is recovery of the ability to do as many activities of daily living (ADLs) as possible. Results of rehabilitation depend on the nature of the loss and the patient's motivation. Progress may be slow for elderly patients and for patients who lack muscle strength or motivation.

Rehabilitation may begin in an acute care hospital. Rehabilitation hospitals or units usually provide the most extensive and intensive care; they should be considered for patients who have good potential for recovery and can participate in and tolerate aggressive therapy (generally, ≥ 3 h/day). Many nursing homes have less intensive programs (generally, 1 to 3 h/day, up to 5 days/wk) and thus are better suited to patients less able to tolerate therapy (eg, frail or elderly patients). Less varied and less frequent rehabilitation programs may be offered in outpatient settings or at home and are appropriate for many patients. However, outpatient rehabilitation can be relatively intensive (several hours/day up to 5 days/wk).

An interdisciplinary approach is best because disability can lead to various problems (eg, depression, lack of motivation to regain lost function, financial problems). Thus, patients may require psychologic intervention and help from social workers or mental health practitioners. Also, family members may need help learning how to adjust to the patient's disability and how to help the patient.

Referral: To initiate formal rehabilitation therapy, a physician must write a referral/prescription to a physiatrist, therapist, or rehabilitation center. The referral/prescription should state the diagnosis and goal of therapy. The diagnosis may be specific (eg, after left-sided stroke, residual right-sided deficits in upper and lower extremities) or functional (eg, generalized weakness due to bed rest). Goals should be as specific as possible (eg, training to use a prosthetic limb, maximizing general muscle strength and overall endurance). Although vague instructions (eg, physical therapy to evaluate and treat) are sometimes accepted, they are not in the patients' best interests and may be rejected with a request for more specific instructions. Physicians unfamiliar with writing referrals for rehabilitation can consult a physiatrist.

Goals of therapy: Initial evaluation sets goals for restoring mobility and functions needed to do ADLs, which include caring for self (eg, grooming, bathing, dressing, feeding, toileting), cooking, cleaning, shopping, managing drugs, managing finances, using the telephone, and traveling. The referring physician and rehabilitation team determine which activities are achievable and which are essential for the patient's independence. Once ADL function is maximized, goals that can help improve quality of life are added.

Patients improve at different rates. Some courses of therapy last only a few weeks; others last longer. Some patients who have completed initial therapy need additional therapy.

Patient and caregiver issues: Patient and family education is an important part of the rehabilitation process, particularly when the patient is discharged into the community. Often, the nurse is the team member primarily responsible for this education. Patients are taught how to maintain newly regained functions and how to reduce the risk of accidents (eg, falls, cuts, burns) and secondary disabilities. Family members are taught how to help the patient be as independent as possible, so that they do not overprotect the patient (leading to decreased functional status and increased dependence) or neglect the patient's primary needs (leading to feelings of rejection, which may cause depression or interfere with physical functioning).

Emotional support from family members and friends is essential. It may take many forms. Spiritual support and counseling by peers or by religious advisors can be indispensable for some patients.

Geriatric Rehabilitation

Disorders requiring rehabilitation (eg, stroke, MI, hip fracture, limb amputation) are common among the elderly. The elderly are also more likely to have become deconditioned before the acute problem that necessitates rehabilitation.

The elderly, even if cognitively impaired, can benefit from rehabilitation. Age alone is not a reason to postpone or deny rehabilitation. However, the elderly may recover slowly because of a reduced ability to adapt to a changing environment, including

- Physical inactivity
- Lack of endurance
- Depression or dementia
- Decreased muscle strength, joint mobility, coordination, or agility
- Impaired balance

Programs designed specifically for the elderly are preferable because the elderly often have different goals, require less intensive rehabilitation, and need different types of care than do younger patients. In age-segregated programs, elderly patients are less likely to compare their progress with that of younger patients and to become discouraged, and the social work aspects of postdischarge care can be more readily integrated. Some programs are designed for specific clinical situations (eg, recovery from hip fracture surgery); patients with similar conditions can work together toward common goals by encouraging each other and reinforcing the rehabilitation training.

Physical Therapy

Physical therapy aims to improve joint and muscle function (eg, range of motion, strength) and thus improve the patient's ability to stand, balance, walk, and climb stairs. For example, physical therapy is usually used to train lower-extremity amputees. On the other hand, occupational therapy (see p. 3456) focuses on self-care activities and improvement of fine motor coordination of muscles and joints, particularly in the upper extremities.

Range of motion: Limited range of motion impairs function and tends to cause pain and to predispose patients to pressure ulcers. Range of motion should be evaluated with a goniometer before therapy and regularly thereafter (for normal values, see Table 350-1).

Range-of-motion exercises stretch stiff joints. Stretching is usually most effective and least painful when tissue temperature is raised to about 43° C (see p. 3459). There are several types:

- **Active:** This type is used when patients can exercise without assistance; patients must move their limbs themselves.
- **Active assistive:** This type is used when muscles are weak or when joint movement causes discomfort; patients must move their limbs, but a therapist helps them do so.
- **Passive:** This type is used when patients cannot actively participate in exercise; no effort is required from them.

Strength and conditioning: Many exercises aim to improve muscle strength (for grading muscle strength, see Table 350-2). Muscle strength may be increased with progressive resistive exercise. When a muscle is very weak, gravity alone is sufficient resistance. When muscle strength becomes fair, additional manual or mechanical resistance (eg, weights, spring tension) is added.

General conditioning exercises combine various exercises to treat the effects of debilitation, prolonged bed rest, or immobilization. The goals are to reestablish hemodynamic balance, increase cardiorespiratory capacity and endurance, and maintain range of motion and muscle strength.

For the elderly, the purpose of these exercises is both to strengthen muscles enough to function normally and possibly to regain normal strength for age.

Proprioceptive neuromuscular facilitation: This technique helps promote neuromuscular activity in patients who have upper motor neuron damage with spasticity; it enables them to feel muscle contraction and helps maintain the affected joint's range of motion. For example, applying strong resistance to the left elbow flexor (biceps) of patients with right hemiplegia causes the hemiplegic biceps to contract, flexing the right elbow.

[**Table 350-1.** Normal Values for Range of Motion of Joints*]

[**Table 350-2.** Grades of Muscle Strength]

Coordination exercises: These task-oriented exercises improve motor skills by repeating a movement that works more than one joint and muscle simultaneously (eg, picking up an object, touching a body part).

Ambulation exercises: Before proceeding to ambulation exercises, patients must be able to balance in a standing position. Balancing exercise is usually done using parallel bars with a therapist standing in front of or directly behind a patient. While holding the bars, patients shift weight from side to side and from forward to backward. Once patients can balance safely, they can proceed to ambulation exercises.

Ambulation is often a major goal of rehabilitation. If individual muscles are weak or spastic, an orthosis (eg, a brace) may be used (see p. 3457). Ambulation exercises are commonly started using parallel bars; as patients progress, they use a walker, crutches, or cane and then walk without devices. Some patients wear an assistive belt used by the therapist to help prevent falls. Anyone assisting patients with ambulation should know how to correctly support them (see Fig. 350-1).

As soon as patients can walk safely on level surfaces, they can start training to climb stairs or to step over curbs if either skill is needed. Patients who use walkers must learn special techniques for climbing stairs and stepping over curbs. When climbing stairs, ascent starts with the better leg, and descent starts with the affected leg (ie, good leads up; bad leads down). Before patients are discharged, the social worker or physical therapist should arrange to have secure handrails installed along all stairs in the patients' home.

Transfer training: Patients who cannot transfer independently from bed to chair, chair to commode, or chair to a standing position usually require attendants 24 h/day. Adjusting the heights of commodes and chairs may help. Sometimes assistive devices are useful; eg, people who have difficulty standing from a seated position may benefit from a chair with a raised seat or a self-lifting chair.

[**Fig. 350-1.** Supporting a patient during ambulation.]

Occupational Therapy

Occupational therapy (OT) focuses on self-care activities and improvement of fine motor coordination of muscles and joints, particularly in the upper extremities. Unlike physical therapy, which focuses on muscle strength and joint range of motion, OT focuses on activities of daily living (ADLs) because they are the cornerstone of independent living. Basic ADLs (BADLs) include eating, dressing, bathing, grooming, toileting, and transferring (ie, moving between surfaces such as the bed, chair, and bathtub or shower). Instrumental ADLs (IADLs) require more complex cognitive functioning than BADLs. IADLs include preparing meals; communicating by telephone, writing, or computer; managing finances and daily drug regimens; cleaning; doing laundry, food shopping, and other errands; managing finances; traveling as a pedestrian or by public transportation; and driving. Driving is particularly complex, requiring integration of

visual, physical, and cognitive tasks.

Evaluation: OT can be initiated when a physician writes a referral for rehabilitation, which is similar to writing a prescription. The referral should be detailed, including a brief history of the problem (eg, type and duration of the disorder or injury) and establishing the goals of therapy (eg, training in IADLs). Lists of occupational therapists may be obtained from a patient's insurance carrier, a local hospital, the telephone book, state occupational training organizations, or the web site of the American Occupational Therapy Association.

Patients are evaluated for limitations that require intervention and for strengths that can be used to compensate for weaknesses. Limitations may involve motor function, sensation, cognition, or psychosocial function. Examiners determine which activities (eg, work, leisure, social, learning) patients want or need help with. Patients may need help with a general type of activity (eg, social) or a specific activity (eg, attending church), or they may need to be motivated to do an activity. Therapists may use an assessment instrument to help in the evaluation. One of the many functional assessment instruments is described in Table 350-3. Patients are asked about their social and family roles, habits, and social support systems. The availability of resources (eg, community programs and services, private attendants) should be determined.

Occupational therapists may also assess the home for hazards and make recommendations to ensure home safety (eg, removing throw rugs, increasing hallway and kitchen lighting, moving a night table within reach of the bed, placing a family picture on a door to help patients recognize their room).

Determining when driving is a risk and whether driver retraining is indicated is best done by occupational therapists with specialized training. Information that can help elderly drivers and their caregivers in coping with changing driving abilities is available from the American Occupational Therapy Association and the American Association for Retired Persons.

Interventions: OT may consist of one consultation or frequent sessions of varying intensity. Sessions may occur in various settings:

• Acute care, rehabilitation, outpatient, adult day care, skilled nursing, or long-term care facilities

• The home (as part of home health care)

• Senior housing developments

• Life-care or assisted-living communities

Occupational therapists develop an individualized program to enhance patients' motor, cognitive, communication, and interaction capabilities. The goal is not only to help patients do ADLs but also to do appropriate preferred leisure activities and to foster and maintain social integration and participation.

Before developing a program, a therapist observes patients doing each activity of the daily routine to learn what is needed to ensure safe, successful completion of the activities. Therapists can then recommend ways to eliminate or reduce maladaptive patterns and to establish routines that promote function and health. Specific performance-oriented exercises are also recommended. Therapists emphasize that exercises must be practiced and motivate patients to do so by focusing on exercise as a means of becoming more active at home and in the community.

Patients are taught creative ways to facilitate social activities (eg, how to get to museums or church without driving, how to use hearing aids or other assistive communication devices in different settings, how to travel safely with or without a cane or walker). Therapists may suggest new activities (eg, volunteering in foster grandparent programs, schools, or hospitals).

Patients are taught strategies to compensate for their limitations (eg, to sit when gardening). The therapist may identify various assistive devices that can help patients do many activities of daily living (see

Table 350-4). Most occupational therapists can select wheelchairs appropriate for patients' needs and provide training for upper-extremity amputees.

[**Table 350-3.** Katz Activities of Daily Living Scale]

Occupational therapists may construct and fit devices to prevent contractures and treat other functional disorders.

Speech Therapy

Speech therapists can identify the most effective methods of communication for patients who have aphasia, dysarthria, or verbal apraxia or who have had a laryngectomy:

- Expressive aphasia: A letter or picture board
- Mild to moderate dysarthria or apraxia: Breathing and muscle control plus repetition exercises
- Severe dysarthria or apraxia: An electronic device with a keyboard and message display (print or screen)
- Postlaryngectomy: A new way to produce a voice (eg, by an electrolarynx—see p. 490)

Therapeutic and Assistive Devices

Orthoses provide support for damaged joints, ligaments, tendons, muscles, and bones. Most are customized to a patient's needs and anatomy. Orthoses designed to fit into shoes may shift the patient's weight to different parts of the foot to compensate for lost function, prevent deformity or injury, help bear weight, or relieve pain, as well as provide support. Orthoses are often very expensive and not covered by insurance.

Walking aids include walkers, crutches, and canes (see Fig. 350-2). They help with weight

[**Table 350-4.** Assistive Devices]

bearing, balance, or both. Each device has advantages and disadvantages, and each is available in many models. After evaluation, a therapist should choose the one that provides the best combination of stability and freedom for the patient (see Table 350-5). Physicians should know how to fit crutches (see Fig. 350-3). Prescriptions for assistive devices should be as specific as possible.

Wheelchairs provide mobility to patients who cannot walk. Some models are designed to be self-propelled and to provide stability for traveling over uneven ground and up and down curbs. Other models are designed to be pushed by an assistant; they provide less stability and speed. Wheelchairs are available with various features. For athletic patients with impaired lower extremities but good upper body strength, racing wheelchairs are available. A one-arm-drive or hemi-height wheelchair may be suitable for hemiplegic patients with good coordination. If patients have little or no arm function, a motorized wheelchair is prescribed. Wheelchairs for quadriplegics may have chin or mouth (sip and puff) controls and built-in ventilators.

Prostheses are artificial body parts, most commonly limbs designed to replace lower or upper extremities after amputation (see p. 3465). Technical innovations have greatly improved the comfort and functionality of prostheses. Many prostheses can be cosmetically altered to appear natural. A prosthetist should be involved early to help patients understand the many options in prosthetic design, which should meet the patients' needs and safety requirements. Many patients can expect to regain considerable function. Physical therapy

[**Table 350-5.** Ambulation Aids]

should be started even before the prosthesis is fitted; therapy should continue until patients can function with the new limb. Some patients seem unable to tolerate a prosthesis or complete the physical rehabilitation required to successfully use it.

Treatment of Pain and Inflammation

(See also Ch. 171)

Treatment of pain and inflammation aims to facilitate movement and improve coordination of muscles and joints. Nondrug treatments include therapeutic exercise, heat, cold, electrical stimulation, cervical traction, massage, and acupuncture. These treatments are used for many disorders of muscles, tendons, and ligaments (see
Table 350-6). Prescribers should include the following:

• Diagnosis

• Type of treatment (eg, ultrasound, hot pack)

• Location of application (eg, right shoulder, low back)

• Frequency (eg, once/day, every other day)

• Duration (eg, 10 days, 1 wk)

Heat: Heat provides temporary relief in subacute and chronic traumatic and inflammatory disorders (eg, sprains, strains, fibrositis, tenosynovitis, muscle spasm, myositis, back pain, whiplash injuries, various forms of arthritis, arthralgia, neuralgia). Heat increases blood flow and the extensibility of connective tissue; heat also decreases joint stiffness, pain, and muscle spasm and helps relieve inflammation, edema, and exudates. Heat application may be superficial (infrared heat, hot packs, paraffin bath, hydrotherapy) or deep (ultrasound). Intensity and duration of the physiologic effects depend mainly on tissue temperature, rate of temperature elevation, and area treated.

Infrared heat is applied with a heat lamp, usually for 20 min/day. Contraindications include any advanced heart disorder, peripheral vascular disease, impaired skin sensation (particularly to temperature and pain), and significant hepatic or renal insufficiency. Precautions must be taken to avoid burns.

Hot packs are cotton cloth containers filled with silicate gel; they are boiled in water or

[**Fig. 350-2.** Correct cane height.]

warmed in a microwave oven, then applied to the skin. The packs must not be too hot. Wrapping the packs in several layers of towels helps protect the skin from burns. Contraindications are the same as those for infrared heat.

For a **paraffin bath,** the affected area is dipped in, immersed in, or painted with melted wax that has been heated to 49° C. The heat can be retained by wrapping the affected area with towels for 20 min. Paraffin is usually applied to small joints—typically, by dipping or immersion for a hand and by painting for a knee or an elbow. Paraffin should not be applied to open wounds or used on patients allergic to it. A paraffin bath is particularly useful for finger arthritis.

Hydrotherapy may be used to enhance wound healing. Agitated warm water stimulates blood flow and debrides burns and wounds. This treatment is often given in a Hubbard tank (a large industrial whirlpool) with water heated to 35.5 to 37.7° C. Total immersion in water heated to 37.7 to 40° C may also help relax muscles and relieve pain. Hydrotherapy is particularly useful with range-of-motion exercises.

[**Fig. 350-3.** Fitting crutches.]

Diathermy is therapeutic heating of tissues using oscillating high-frequency electromagnetic fields, either short-wave or microwave. These modalities do not seem superior to simpler forms of heating and are now seldom used.

Ultrasound uses high-frequency sound waves to penetrate deep (4 to 10 cm) into the tissue; its effects are thermal, mechanical, chemical, and biologic. It is indicated for tendinitis, bursitis, contractures, osteoarthritis, bone injuries, and complex regional pain syndrome. Ultrasound should not be applied to ischemic tissue, anesthetized areas, or areas of acute infection nor be used to treat hemorrhagic diathesis or cancer. Also, it should not be applied over the eyes, brain, spinal cord, ears, heart, reproductive organs, brachial plexus, or bones that are healing.

Cold: The choice between heat and cold therapies is often empiric. When heat does not work, cold is applied. However, for acute injury or pain, cold seems to be better than heat. Cold may help relieve muscle spasm, myofascial or traumatic pain, acute low back pain, and acute inflammation; cold may also help induce some local anesthesia. Cold is usually used during the first few hours or the day after an injury; consequently, it is seldom used in physical therapy.

Cold may be applied locally using an ice bag, a cold pack, or volatile fluids (eg, ethyl chloride, vapocoolant spray), which cool by evaporation. Spread of cold on the skin depends on the thickness of the epidermis, underlying fat and muscle, water content of the tissue, and rate of blood flow. Care must be taken to avoid tissue damage and hypothermia. Cold should not be applied over poorly perfused areas.

Electrical stimulation: Transcutaneous electrical nerve stimulation (TENS) uses low current at low-frequency oscillation to relieve pain. Patients feel a gentle tingling sensation without increased muscle tension. Depending on the severity of pain, 20 min to a few hours of stimulation may be applied several times daily. Often, patients are taught to use the TENS device and decide when to apply treatment. Because TENS may cause arrhythmia, it is contraindicated in patients with any advanced heart disorder or a pacemaker. It should not be applied over the eyes.

[**Table 350-6.** Indications for Nondrug Pain Treatments]

Cervical traction: Cervical traction is often indicated for chronic neck pain due to cervical spondylosis, disk prolapse, whiplash injuries, or torticollis. Vertical traction (with patients in a sitting position) is more effective than horizontal traction (with patients lying in bed). Motorized intermittent rhythmic traction with 7.5 to 10 kg is most effective. For best results, traction should be applied with the patient's neck flexed 15 to 20°. Generally, hyperextension of the neck should be avoided because it may increase nerve root compression in the intervertebral foramina. Traction is usually combined with other physical therapy, including exercises and manual stretching.

Massage: Massage may mobilize contracted tissues, relieve pain, and reduce swelling and induration associated with trauma (eg, fracture, joint injury, sprain, strain, bruise, peripheral nerve injury). Massage should be considered for low back pain, arthritis, periarthritis, bursitis, neuritis, fibromyalgia, fibrositis, hemiplegia, paraplegia, quadriplegia, multiple sclerosis, cerebral palsy, and certain types of cancer. Massage should not be used to treat infections or thrombophlebitis. It is not advised for patients with severe allergies because it causes histamine to be released throughout the body. Only a licensed or certified massage therapist should use massage for treatment of an injury because of variability in therapists' training and skills.

Acupuncture: Thin needles are inserted through the skin at specific body sites, frequently far from the site of pain (see p. 3419). Acupuncture is sometimes used with other treatments to manage acute and chronic pain.

Cardiovascular Rehabilitation

Rehabilitation may benefit some patients who have coronary artery disease or heart failure or who have had a recent MI or coronary artery bypass surgery, particularly those who could do activities of daily living independently and walk before the event. Cardiac rehabilitation aims to help patients maintain or regain

independence (see p. 2117).

Typically, rehabilitation begins with light activities and progresses on an individualized basis; ECG monitoring is often used. High-risk patients should exercise only in a well-equipped cardiovascular rehabilitation facility under the supervision of a trained attendant.

When patients are able, they are taken by wheelchair to a physical therapy gym in the hospital. Exercise may involve walking, a treadmill, or a stationary bicycle. When patients tolerate these exercises well, they progress to stair-climbing. If shortness of breath, light-headedness, or chest pain occurs during exercise, the exercise should be stopped immediately, and cardiac status should be reassessed. Before hospital discharge, patients are assessed so that an appropriate postdischarge rehabilitation program or exercise regimen can be recommended.

Physical activity is measured in metabolic equivalents (METs), which are multiples of the resting rate of O_2 consumption; 1 MET (the resting rate) equals about 3.5 mL/kg/min of O_2 (see Tables 350-7). Normal working and living activities (excluding recreational activities) rarely exceed 6 METs. Light to moderate housework is about 2 to 4 METs; heavy housework or yard work is about 5 to 6 METs.

For hospitalized patients, physical activity should be controlled so that heart rate remains < 60% of maximum for that age (eg, about 160 beats/min for people aged 60); for patients recovering at home, heart rate should remain < 70% of maximum.

For patients who have had an uncomplicated MI, a 2-MET exercise test may be done to evaluate responses as soon as patients are stable. A 4- to 5-MET exercise test done before discharge helps guide physical activity at home. Patients who can tolerate a 5-MET exercise test for 6 min can safely do low-intensity activities (eg, light housework) after discharge if they rest sufficiently between each activity.

Unnecessary restriction of activity is detrimental to recovery. The physician and other members of the rehabilitation team should explain which activities can be done and which cannot and should provide psychologic support. When discharged, patients can be given a detailed home activity program. Most elderly patients can be encouraged to resume sexual activity, but they need to stop and rest if necessary to avoid overexertion. Young couples expend 5 to 6 METs during intercourse; whether elderly couples expend more or less is unknown.

Stroke Rehabilitation

Rehabilitation after stroke aims to preserve or improve range of motion, muscle strength, bowel and bladder function, and functional and cognitive abilities. Specific programs are based on the patient's social situation (eg, prospects of returning to home or work), ability

[**Table 350-7.** Endurance Exercises and Their Metabolic Requirement]

to participate in a rehabilitation program supervised by nurses and therapists, learning ability, motivation, and coping skills. A stroke that impairs comprehension often makes rehabilitation very difficult.

To prevent secondary disabilities (eg, contractures) and help prevent depression, rehabilitation should begin as soon as patients are medically stable. Preventive measures for pressure ulcers must be started even before patients are medically stable. Patients can safely begin sitting up once they are fully conscious and neurologic deficits are no longer progressing, usually ≤ 48 h after the stroke. Early in the rehabilitation period, when the affected extremities are flaccid, each joint is passively exercised through the normal range of motion (see Table 350-1) 3 to 4 times/day.

Regaining the ability to get out of bed and to transfer to a chair or wheelchair safely and independently is important for the patient's psychologic and physical well-being. Ambulation problems, spasticity, visual field defects (eg, hemianopia), incoordination, and aphasia require specific therapy.

Hemiplegia: For patients with hemiplegia, placing 1 or 2 pillows under the affected arm can prevent

dislocation of the shoulder. If the arm is flaccid, a well-constructed sling can prevent the weight of the arm and hand from overstretching the deltoid muscle and subluxating the shoulder. A posterior foot splint applied with the ankle in a 90° position can prevent equinus deformity (talipes equinus) and footdrop.

Resistive exercise for hemiplegic extremities may increase spasticity and thus is controversial. However, reeducation and coordination exercises of the affected extremities are added as soon as tolerated, often within 1 wk. Active and active-assistive range-of-motion exercises are started shortly afterward to maintain range of motion. Active exercise of the unaffected extremities must be encouraged, as long as it does not cause fatigue. Various activities of daily living (eg, moving in bed, turning, changing position, sitting up) should be practiced. For hemiplegic patients, the most important muscle for ambulation is the unaffected quadriceps. If weak, this muscle must be strengthened to assist the hemiplegic side.

A gait abnormality in hemiplegic patients is caused by many factors (eg, muscle weakness, spasticity, distorted body image) and is thus difficult to correct. Also, attempts to correct gait often increase spasticity, may result in muscle fatigue, and may increase the already high risk of falls, which often result in a hip fracture; functional prognosis of hemiplegic patients with a hip fracture is very poor. Consequently, as long as hemiplegic patients can walk safely and comfortably, gait correction should not be tried.

Novel treatments for hemiplegia include the following:

- **Constraint-induced movement therapy:** The functional limb is restrained during waking hours, except during specific activities, and patients are forced to do tasks mainly with the affected extremity.

- **Robotic therapy:** Robotic devices are used to provide intensive repetition of the therapeutic movement, guide an affected extremity in executing the movement, provide feedback (eg, on a computer screen) for patients, and measure patient progress.

- **Partial weight-supported ambulation:** A device (eg, treadmill) that bears part of a patient's weight is used during ambulation. The amount of weight borne and speed of ambulation can be adjusted. This approach is often used with robotics, which allows patients to contribute to ambulation but provides force as needed for ambulation.

- **Total body vibration:** Patients stand on an exercise machine with a platform that vibrates by rapidly shifting weight from one foot to the other. The movement stimulates reflexive muscle contraction.

Ambulation problems: Before ambulation exercises can be started, patients must be able to stand. Patients first learn to stand from the sitting position. The height of the seat may need to be adjusted. Patients must stand with the hips and knees fully extended, leaning slightly forward and toward the unaffected side. Using the parallel bars is the safest way to practice standing.

The goal of ambulation exercises is to establish and maintain a safe gait, not to restore a normal gait. Most hemiplegic patients have a gait abnormality, which is caused by many factors (eg, muscle weakness, spasticity, distorted body image) and is thus difficult to correct. Also, attempts to correct gait often increase spasticity, may result in muscle fatigue, and may increase the already high risk of falls.

During ambulation exercises, patients place the feet > 15 cm (6 in) apart and grasp the parallel bars with the unaffected hand. Patients take a shorter step with the hemiplegic leg and a longer step with the unaffected leg. Patients who begin walking without the parallel bars may need physical assistance from and later close supervision by the therapist. Generally, patients use a cane or walker when first walking without the parallel bars. The diameter of the cane handle should be large enough to accommodate an arthritic hand.

For stair-climbing, ascent starts with the better leg, and descent with the affected leg (good leads up; bad leads down). If possible, patients ascend and descend with the railing on the unaffected side, so that they can grasp the railing. Looking up the staircase may cause vertigo and should be avoided. During descent, patients should use a cane. The cane should be moved to the lower step shortly before descending with the bad leg.

Patients must learn to prevent falls, which are the most common accident among stroke patients and which often result in hip fracture. Usually, patients explain the fall by saying that their knees gave way. For hemiplegic patients, who almost always fall on their hemiplegic side, leaning their affected side against a railing (when standing or climbing stairs) can help prevent falls. Doing strengthening exercises for weak muscles, particularly in the trunk and legs, can also help.

For patients with symptomatic orthostatic hypotension, treatment includes support stockings, drugs, and tilt table training. Because hemiplegic patients are prone to vertigo, they should change body position slowly and take a moment after standing to establish equilibrium before walking. Comfortable, supportive shoes with rubber soles and with heels ≤ 2 cm (3/4 in) should be worn.

Spasticity: In some stroke patients, spasticity develops. Spasticity may be painful and debilitating. Slightly spastic knee extensors can lock the knee during standing or cause hyperextension (genu recurvatum), which may require a knee brace with an extension stop. Resistance applied to spastic plantar flexors causes ankle clonus; a short leg brace without a spring mechanism minimizes this problem.

Flexor spasticity develops in most hemiplegic hands and wrists. Unless patients with flexor spasticity do range-of-motion exercises several times a day, flexion contracture may develop rapidly, resulting in pain and difficulty maintaining personal hygiene. Patients and family members are taught to do these exercises, which are strongly encouraged. A hand or wrist splint may also be useful, particularly at night. One that is easy to apply and clean is best.

Heat or cold therapy can temporarily decrease spasticity and allow the muscle to be stretched. Hemiplegic patients may be given benzodiazepines to minimize apprehension and anxiety, particularly during the initial stage of rehabilitation, but not to reduce spasticity. The effectiveness of long-term benzodiazepine therapy for reducing spasticity is questionable. Methocarbamol has limited value in relieving spasticity and causes sedation.

Hemianopia: Patients with hemianopia (defective vision or blindness in half the visual field of one or both eyes) should be made aware of it and taught to move their heads toward the hemiplegic side when scanning. Family members can help by placing important objects and by approaching the patient on the patient's unaffected side. Repositioning the bed so that patients can see a person entering the room through the doorway may be useful. While walking, patients with hemianopia tend to bump into the door frame or obstacles on the hemiplegic side; they may need special training to avoid this problem.

When reading, patients who have difficulty looking to the left may benefit from drawing a red line on the left side of the newspaper column. When they reach the end of a line of text, they scan to the left of the column until they see the red line, cueing them to begin reading the next line. Using a rule to keep focused on each line of text may also help.

Occupational therapy: After a stroke, fine coordination may be absent, causing patients to become frustrated. Occupational therapists may need to modify patients' activities and recommend assistive devices (see Table 350-4).

Occupational therapists should also evaluate the home for safety and determine the extent of social support. They can help obtain any necessary devices and equipment (eg, bathtub bench, grab bars by the bathtub or toilet). Occupational therapists can also recommend modifications that enable patients to do activities of daily living (ADLs) as safely and independently as possible—for example, rearranging the furniture in living areas and removing clutter. Patients and caretakers are taught how to transfer between surfaces (eg, shower, toilet, bed, chair) and, if necessary, how to modify ways of doing ADLs. For example, patients may be taught to dress or shave using only one hand and to eliminate unnecessary motion while preparing food or shopping for groceries. Therapists may suggest using clothing and shoes with touch fasteners (eg, Velcro) or dinner plates with rims and rubber grips (to facilitate handling). Patients with impairments in cognition and perception are taught ways to compensate. For example, they can use drug organizers (eg, containers marked for each day of the week).

Leg Amputation Rehabilitation

Before amputation, the physician describes to the patient the extensive postsurgical rehabilitation program that is needed. Psychologic counseling may be indicated. The rehabilitation team and the patient decide whether a prosthesis or a wheelchair is needed.

Rehabilitation teaches ambulation skills; it includes exercises to improve general conditioning and balance, to stretch the hip and knee, to strengthen all extremities, and to help patients tolerate the prosthesis. Because ambulation requires a 10 to 40% increase in energy expenditure after below-the-knee amputation and a 60 to 100% increase after above-the-knee amputation, endurance exercises may be indicated. As soon as patients are medically stable, rehabilitation should be started to help prevent secondary disabilities. Elderly patients should begin standing and doing balancing exercises with parallel bars as soon as possible.

Flexion contracture of the hip or knee may develop rapidly, making fitting and using the prosthesis difficult; contractures can be prevented with extension braces made by occupational therapists.

Physical therapists teach patients how to care for the stump and how to recognize the earliest signs of skin breakdown.

Stump Conditioning and Prostheses

Stump conditioning promotes the natural process of stump shrinking that must occur before a prosthesis can be used. After only a few days of conditioning, the stump may have shrunk greatly. An elastic stump shrinker or elastic bandages worn 24 h/day can help taper the stump and prevent edema. The stump shrinker is easy to apply, but bandages may be preferred because they better control the amount and location of pressure. However, application of elastic bandages requires skill, and bandages must be reapplied whenever they become loose.

Early ambulation with a temporary prosthesis helps in the following ways:

• Enables the amputee to be active

• Accelerates stump shrinkage

• Prevents flexion contracture

• Reduces phantom limb pain

The socket of the pylon (the internal framework or skeleton of a prosthesis) is made of plaster of paris (calcium sulfate hemihydrate); it should fit the stump snugly. Various temporary prostheses with adjustable sockets are available. Patients with a temporary prosthesis can start ambulation exercises on the parallel bars and progress to walking with crutches or canes until a permanent prosthesis is made.

The permanent prosthesis should be lightweight and meet the needs and safety requirements of the patient. If the prosthesis is made before the stump stops shrinking, adjustments may be needed. Therefore, manufacture of a permanent prosthesis is generally delayed a few weeks to allow shrinkage of the stump. For most elderly patients with a below-the-knee amputation, a patellar tendon-bearing prosthesis with a solid-ankle, cushion-heel foot, and suprapatellar cuff suspension is best. Unless patients have special needs, a below-the-knee prosthesis with thigh corset and waist belt is not prescribed because it is heavy and bulky. For above-the-knee amputees, several knee-locking options are available according to the patient's skills and activity level.

Care of the stump and prosthesis: Patients must learn to care for their stump. Because a leg prosthesis is intended only for ambulation, patients should remove it before going to sleep. At bedtime, the stump should be inspected thoroughly (with a mirror if inspected by the patient), washed with mild soap and warm water, dried thoroughly, then dusted with talcum powder. Patients should treat the following possible problems:

- Dry skin: Lanolin or petrolatum may be applied to the stump.

- Excessive sweating: An unscented antiperspirant may be applied.

- Inflamed skin: The irritant must be removed immediately, and talcum powder or a lowpotency corticosteroid cream or ointment should be applied.

- Broken skin: The prosthesis should not be worn until the wound has healed.

The stump sock should be changed daily, and mild soap may be used to clean the inside of the socket. Standard prostheses are neither waterproof nor water-resistant. Therefore, if even part of the prosthesis becomes wet, it must be dried immediately and thoroughly; heat should not be applied. For patients who swim or prefer to shower with a prosthesis, a prosthesis that can tolerate immersion can be made.

Complications

Stump pain is the most common complaint. Common causes include

- A poorly fitted prosthetic socket: This cause is the most common.

- Neuroma: An amputation neuroma is usually palpable. Daily ultrasound treatment for 5 to 10 sessions may be most effective. Other treatments include injection of corticosteroids or analgesics into the neuroma or the surrounding area, cryotherapy, and continuous tight bandaging of the stump. Surgical resection often has disappointing results.

- Spur formation at the amputated end of the bone: Spurs may be diagnosed by palpation and x-ray. The only effective treatment is surgical resection.

Phantom limb sensation (a painless awareness of the amputated limb possibly accompanied by tingling) is experienced by some new amputees. This sensation may last several months or years but usually disappears without treatment. Frequently, patients sense only part of the missing limb, often the foot, which is the last phantom sensation to disappear. Phantom limb sensation is not harmful; however, patients, without thinking, commonly attempt to stand with both legs and fall, particularly when they wake at night to go to the bathroom.

Phantom limb pain is less common and can be severe and difficult to control. Some experts think it is more likely to occur if patients had a painful condition before amputation or if pain was not adequately controlled intraoperatively and postoperatively. Various treatments, such as simultaneous exercise of amputated and contralateral limbs, massage of the stump, finger percussion of the stump, use of mechanical devices (eg, a vibrator), and ultrasound, are reportedly effective. Drugs (eg, gabapentin) may help.

Skin breakdown tends to occur because the prosthesis presses on and rubs the skin and because moisture collects between the stump and prosthetic socket. Skin breakdown may be the first indication that the prosthesis needs adjustment and needs to be managed immediately. The first sign of skin breakdown is redness; then cuts, blisters, and sores may develop, the prosthesis is often painful or impossible to wear for long periods of time, and infection can develop. Several measures can help prevent or delay skin breakdown:

- Having an interface that fits well

- Maintaining a stable body weight (even small changes in weight can affect fit)

- Eating a healthy diet and drinking lots of water (to control body weight and maintain healthy skin)

- For patients with diabetes, monitoring and controlling their blood sugar level (to help prevent vascular disease and thus maintain blood flow to the skin)

• For patients with a lower-limb prosthesis, maintaining body alignment (eg, wearing only shoes with a similar heel height)

However, even with a good fit, problems can occur. The stump changes in shape and size throughout a day, depending on activity level, diet, and the weather. Thus, there are times when the interface fits well and times when it fits less well. In response to such ongoing changes, people can help maintain a good fit by switching to a thicker or thinner liner or sock, by using a liner and a sock, or by adding or removing thin-ply socks. But even so, the stump's size may vary enough to cause skin breakdown. If there are signs of skin breakdown, patients should promptly see a health care practitioner and a prosthetist; when possible they should also avoid wearing the prosthesis until it can be adjusted.

Hip Surgery Rehabilitation

Rehabilitation is started as soon as possible after hip fracture surgery. The first goals may be to increase strength and to prevent atrophy on the unaffected side. Initially, only isometric exercise of the affected limb while it is fully extended is permitted. Placement of a pillow under the knee is contraindicated because it may lead to flexion contracture of the hip and knee.

Gradual mobilization of the affected limb usually results in full ambulation. Speed of rehabilitation depends partly on the type of surgery done. For example, after prosthetic hip replacement, rehabilitation usually progresses more rapidly, less rehabilitation is needed, and the functional outcome is better than after nail-and-plate or pin-and-plate fixation. Ideally, full weight bearing starts on the 2nd day after surgery. Ambulation exercises are started after 4 to 8 days (assuming that patients can bear their full weight and can balance), and stair-climbing exercises are started after about 11 days.

Patients are taught to do daily exercises to strengthen the trunk muscles and quadriceps of the affected leg. Prolonged lifting or pushing of heavy items, stooping, reaching, or jumping can be harmful. During ambulation, the amount of mechanical stress is about the same whether patients use 1 or 2 canes, but using 2 may interfere with certain activities of daily living (ADLs). Patients should not sit on a chair, particularly a low one, for a long period and should use the chair arm for support when standing up. While sitting, they should keep their legs uncrossed.

Occupational therapists teach patients how to modify ways of doing basic ADLs (BADLs) and instrumental ADLs (IADLs) safely after hip replacement, thus promoting healing and improving mobility. For example, patients may learn the following:

• To keep their hip correctly aligned

• To wash dishes and iron while sitting on a high stool

• To use a pillow to raise the seat of the car while transferring in and out

• To use long-handled devices (eg, reachers, shoe horns) to minimize bending over

This instruction may occur in the hospital, in longer-term rehabilitation settings, in the patient's home immediately after discharge, or in outpatient settings.

Rehabilitation for Other Disorders

Arthritis: Patients with arthritis can benefit from activities and exercises to increase joint range of motion and strength and from strategies to protect the joints. For example, patients may be advised

• To slide a pot of boiling water containing pasta rather than carry it from the stove to the sink (to avoid undue pain and strain to joints)

• How to get in and out of the bathtub safely

• To get a raised toilet seat, a bathtub bench, or both (to reduce pain and stress on the lower-extremity

joints)

- To wrap foam, cloth, or tape around the handles of objects (eg, knives, cooking pots and pans) to cushion the grip

- To use tools with larger, ergonomically designed handles

Such instruction may occur in outpatient settings, in the home via a home health care agency, or in private practice.

Blindness: Patients are taught to rely more on the other senses, to develop specific skills, and to use devices for the blind (eg, Braille, cane, reading machine). Therapy aims to help patients function to their maximum and become independent, to restore psychologic security, and to help patients deal with and influence the attitudes of other people. Therapy varies depending on the way vision was lost (suddenly or slowly and progressively), extent of vision loss, the patient's functional needs, and coexisting deficits. For example, patients with peripheral neuropathy and diminished tactile sensation in the fingers may have difficulty reading Braille. Many blind people need psychologic counseling (usually cognitive-behavioral therapy) to help them better cope with their condition.

For ambulation, therapy may involve learning to use a cane; canes used by the blind are usually white and longer and thinner than ordinary canes. People who use a wheelchair are taught to use one arm to operate the wheelchair and the other to use a cane. People who prefer to use a trained dog instead of a cane are taught to handle and care for the dog. When walking with a sighted person, a blind person can hold onto the bent elbow of the sighted person, rather than use an ambulation aid. The sighted person should not lead the blind person by the hand because some blind people perceive this action as dominant and controlling.

COPD: Patients with COPD can benefit from exercises to increase endurance and from strategies to simplify activities and thus conserve energy. Activities and exercises that encourage use of the upper and lower extremities are used to increase muscle aerobic capacity, which decreases overall oxygen requirement and eases breathing. Supervising patients while they engage in activity helps motivate them and makes them feel more secure. Such instruction may occur in medical facilities or in the patient's home.

Head injury: The term head injury is often used interchangeably with traumatic brain injury (TBI—see p. 3218). Abnormalities vary and may include muscle weakness, spasticity, incoordination, and ataxia; cognitive dysfunction (eg, memory loss, loss of problem-solving skills, language and visual disturbances) is common.

Early intervention by rehabilitation specialists is indispensable for maximal functional recovery (see also p. 3231). Such intervention includes prevention of secondary disabilities (eg, pressure ulcers, joint contractures), prevention of pneumonia, and family education. As early as possible, rehabilitation specialists should evaluate patients to establish baseline findings. Later, before starting rehabilitation therapy, patients should be reevaluated; these findings are compared with baseline findings to help prioritize treatment. Patients with severe cognitive dysfunction require extensive cognitive therapy, which is often begun immediately after injury and continued for months or years.

Spinal cord injury: Specific rehabilitation therapy varies depending on the patient's abnormalities, which depend on the level and extent (partial or complete) of the injury (see Ch. 325, particularly Table 325-1 on p. 3228). Complete transsection causes flaccid paralysis; partial transsection causes spastic paralysis of muscles innervated by the affected segment. A patient's functional capacity depends on the level of injury (see p. 1805) and the development of complications (eg, joint contractures, pressure ulcers, pneumonia).

The affected area must be immobilized surgically or nonsurgically as soon as possible and throughout the acute phase. During the acute phase, daily routine care should include measures to prevent contractures, pressure ulcers, and pneumonia; all measures needed to prevent other complications (eg, orthostatic hypotension, atelectasis, deep venous thrombosis, pulmonary embolism) should also be taken. Placing

patients on a tilt table and increasing the angle gradually toward the upright position may help reestablish hemodynamic balance. Compression stockings, an elastic bandage, or an abdominal binder may prevent orthostatic hypotension.

Chapter 351. Medicolegal Issues

Introduction

Medicine is practiced within an expanding and evolving system of legal rights and obligations, patient protections, health care financing regulation, and standards of care. Thus, health care can involve significant legal issues, including capacity of patients to make health care decisions, confidentiality of medical information, advance directives, and malpractice liability.

Capacity (Competence) and Incapacity

Historically, "incapacity" was considered primarily a clinical finding, and "incompetency" was considered a legal finding. That distinction is no longer firmly recognized; most state laws now use "incapacity" rather than "incompetency," although the terms are frequently used interchangeably. The key distinction now is between clinical incapacity and legal incapacity to make a health care decision.

Patients who have clinical and legal capacity have the right to make health care decisions, including refusal of medically necessary care, even if death may result from refusal. Patients who lack either capacity cannot make health care decisions. However, if a patient deemed by a physician to lack clinical capacity expresses a preference, the physician is not entitled to override that preference unless the patient is also found by a court to lack legal capacity to make that decision.

Clinical capacity: Clinical capacity to make health care decisions is the ability to understand the benefits and risks of the proposed health care, to understand possible alternatives, and to make and communicate a health care decision. Health care practitioners determine this type of capacity clinically and document the determination process. The courts become involved only when the determination itself or another aspect of the process is challenged.

Clinical capacity is specific to a particular health care decision and thus is limited to that decision. The level of clinical capacity needed to make a health care decision depends on the complexity of that decision. Patients with some decrease in capacity, even those with fairly severe cognitive deficits, may still have enough capacity to make simple health care decisions, such as whether to allow a rectal examination or placement of an IV. The same patient may lack the capacity to decide whether to participate in a clinical trial. All feasible attempts should be made to involve the patient in decision making. Ignoring the decision of patients with capacity or accepting the decision of patients without capacity is unethical and risks civil liability. A patient's ability to carry out a decision is also important for physicians to assess. For example, a patient with a broken leg may be able to make decisions but be unable to carry them out. Providing the necessary support to carry out a decision becomes an important goal of care.

Capacity may be intermittent, variable, and affected by the environment. Patients who lack capacity due to intoxication, delirium, coma, severe depression, agitation, or other impairment may regain capacity when their impairment resolves. To obtain consent to treat a patient who lacks clinical capacity, health care practitioners must contact an agent or proxy designated in the patient's durable power of attorney for health care or another legally authorized surrogate (see below). If urgent or emergency care is needed (eg, for an unconscious patient after an acute event) and there is no designated surrogate or the surrogate is unavailable, the doctrine of presumed consent applies: Patients are presumed to consent to any necessary treatment.

Legal capacity: Legal capacity (also called competency) is a legal status; it cannot be determined by health care practitioners. In the US, people aged ≥ 18 yr are automatically considered legally capable of making health care decisions for themselves. Emancipated minors are people below the age of majority (usually 18) who are also considered legally capable. The definition of this group varies by state but generally includes minors who are married, who are in the armed forces, or who have obtained a court decree of emancipation.

People remain legally capable until a judge with appropriate jurisdiction declares them legally incapacitated with respect to some or all areas of functioning. The legal requirements for declaring legal incapacity vary by state. However, substantiation of all of the following is typically required:

- A disabling condition (eg, intellectual disability [mental retardation], a mental disorder, dementia, altered consciousness, chronic use of drugs)

- Inability to receive and evaluate information or to make or communicate decisions

- Inability to meet essential requirements of physical health, safety, or self-care without protective intervention

If physicians question a person's legal capacity, they may seek a court's determination. Physicians may be asked to testify at or provide documentation for a hearing to determine legal capacity.

When the court declares a person legally incapacitated, it appoints a guardian or conservator to make legally binding decisions for the person in a specific range of matters. Courts can also make decisions about disputed issues (eg, the meaning of a particular instruction in the patient's living will about which parties disagree).

Informed Consent

Consent of the patient is a prerequisite for any medical intervention. However, that consent often does not need to be expressed. For emergency care, consent is normally presumed. For interventions considered routine and unlikely to cause harm (eg, routine phlebotomy, placement of an IV line), circumstances are typically considered to imply consent. For example, by holding out their arm, patients are presumed to indicate consent to receive certain routine interventions. For more invasive or risky interventions, express informed consent is always required.

To give informed consent, patients must have legal and clinical capacity (see p. 3468). Health care practitioners obtaining informed consent must be qualified to explain the risks and benefits of the intervention and to answer appropriate questions. The law requires that health care practitioners take reasonable steps to communicate adequately with patients who do not speak English or who have other communication barriers.

Ethical and legal authorities generally agree that health care practitioners are obligated to ensure, at a minimum, that patients understand

- Their current medical status, including its likely course if no treatment is pursued

- Potentially helpful treatments, including a description and explanation of potential risks and benefits

- Usually, the practitioner's professional opinion as to the best alternative

- Uncertainties associated with each of these elements

Generally, these discussions are noted in the medical record, and a document describing the discussion is signed by the patient.

Although practitioners are ethically bound to provide sufficient information and to encourage decisions judged to be in the patient's best interest, patients still have the right to refuse treatment. A patient's refusal of treatment is not considered to be attempted suicide, nor is the health care practitioner's compliance with the patient's wishes legally considered physician-assisted suicide. Rather, the subsequent death is considered legally to be a natural consequence of the disease process itself.

A refusal of care, if puzzling, should prompt the health care practitioner to initiate further discussion. If refusal of treatment will hurt other people, such as a minor child or other dependent, ethical and legal consultation should be sought.

Consent and Surrogate Decision Making

When immediate decisions are medically required, the doctrine of presumed consent applies (see above). In other circumstances, consent must be obtained.

Children: For most nonemergency medical decisions affecting minors, medical care cannot proceed without a parent's or guardian's consent. The parent's or guardian's decision can be overridden only if a court determines that the decision constitutes neglect or abuse of the minor. In some states, minors can consent to certain medical treatments (eg, treatment of sexually transmitted diseases, prescriptions for birth control, abortion) without parental permission. Individual state law must be consulted.

Adults: When adult patients lack capacity to consent to or refuse medical treatment, health care practitioners must rely on an authorized surrogate for consent and decision making. All surrogates —whether appointed by the individual, by default, or by the court—have an obligation to follow the expressed wishes of the patient and to act in the patient's best interests, taking into account the patient's personal values to the extent known.

If adult patients already have a court-appointed guardian with authority to make health care decisions, the guardian is the authorized surrogate. If patients who lack capacity have a durable power of attorney for health care, the agent or proxy appointed by that document is authorized to make health care decisions within the scope of authority granted by the document. Generally, specific instructions that are given in a living will, health care declaration, or other advance directive executed by patients while capacitated can be relied on.

If the decision of an authorized agent or proxy seems to conflict directly with instructions in a living will, the outcome depends on the scope of discretion given to the agent or proxy. Normally, the durable power of attorney for health care confers broad decision-making discretion on the agent. Nevertheless, the health care practitioner should determine whether the document gives the agent broad discretion beyond the written instructions or limits the agent to the written instructions. Legal advice may be needed.

If patients have no authorized surrogate, health care practitioners usually rely on the next of kin or even a close friend. However, the exact scope of authority and the priority of permissible surrogates vary by state. Typically, the order of priority is a spouse (or domestic partner in jurisdictions that recognize this status), an adult child, a parent, a sibling, then possibly other relatives or a close friend. If more than one person has the same priority (eg, several adult children), consensus is preferred, but some states allow health care practitioners to rely on a majority decision.

If a patient's decision-making capacity, a surrogate's authority, or the ethical or legal appropriateness of a particular treatment decision is disputed, consultation with an institutional ethics committee or similar body is advisable. If agreement on an ethically and legally sound resolution cannot be reached, health care practitioners may need to request court review. Many institutions make the ethics committee available on short notice (eg, in 1 or 2 days); judicial review is typically more time-consuming.

Scope: Patient choice is not limitless. For example, health care practitioners are not required to provide treatments that are medically inappropriate, such as those that are against generally accepted health care standards. However, sometimes there are legitimate differences of opinion regarding what is inappropriate. Labeling a treatment as "futile" does not generally help if said treatment may affect outcomes other than mortality or morbidity that are important to the patient. Physicians do not have to act against their conscience, but if they cannot comply with a requested course of action, they may have a responsibility to try to transfer a patient to another physician or institution of the patient's choice.

Confidentiality and HIPAA

Traditionally, ethical health care has always included the need to keep patients' medical information confidential. However, the Health Insurance Portability and Accountability Act (HIPAA—see www.hhs.gov/ocr/hipaa) has codified the responsibility of health care providers. In HIPAA, "health care providers" include health plans, health care clearing-houses, and health care practitioners who electronically conduct financial and administrative transactions (eg, enrollment, billing, eligibility verification). Key provisions of HIPAA involve the following areas.

Access to medical records: Generally, patients should be able to see and obtain copies of their medical records and request corrections if they identify errors.

Notice of privacy practices: Health care providers must provide a notice about their possible uses of personal medical information and about patient rights under HIPAA regulations.

Limits on use of personal medical information: HIPAA limits how health care providers may use individually identifiable (protected) health information. The act does not restrict physicians, nurses, and other practitioners from sharing information needed to treat their patients. However, practitioners may use or share only the minimum amount of protected information needed for a particular purpose. In most situations, personal health information may not be used for purposes unrelated to health care. For example, a patient must sign a specific authorization before a health care provider can release medical information to a life insurer, a bank, a marketing firm, or another outside business for purposes unrelated to the patient's current health care needs.

Marketing: Marketing is communication designed to encourage people to purchase a particular product or service. HIPAA requires that the patient's specific authorization must be obtained before disclosing information for marketing. The health care practitioner must disclose any payments that will be received as a result of marketing. However, health care practitioners can freely communicate with patients about treatment options, products, and other health-related services, including disease-management programs.

Confidential communications: A patient can request that health care practitioners take reasonable steps to ensure that their communications with the patient are confidential. For example, patients could ask a physician to call their office rather than home. Nonetheless, unless the patient objects, practitioners can share medical information with a patient's immediate family members or someone known to be a close personal friend if the information relates directly to that person's involvement with the patient's care or payment for care. Practitioners are expected to exercise professional judgment.

For purposes of the privacy rule, an authorized personal representative of the patient (eg, a proxy appointed in a power of attorney for health care or a state-authorized decision-making surrogate) should be treated the same as the patient. Thus, the representative has the same access to information and may exercise the same rights regarding confidentiality of information. Nevertheless, practitioners may restrict information or access if there are reasonable concerns about domestic violence, abuse, or neglect by the representative.

Some communication cannot remain confidential. Health care practitioners are sometimes required by law to disclose certain information, usually because the condition may present a danger to other people. For example, certain infectious diseases (eg, HIV, syphilis, TB) must be reported to state or local public health agencies. Conditions that might seriously impair a patient's ability to drive, such as dementia or recent seizures, must be reported to the Department of Motor Vehicles in some states.

Complaints: Patients may file complaints about compliance with these privacy practices. Complaints can be made directly to the health care practitioner or to the Office for Civil Rights in the US Department of Health and Human Services. Patients do not have a right to file a private lawsuit under HIPAA. There are civil and criminal penalties for misuse of personal health information; however, such penalties should not worry health care practitioners who, in good faith, make reasonable attempts to comply.

Advance Directives

Advance directives are legal documents that extend a person's control over health care decisions in the event that the person becomes incapacitated. They are called advance directives because they direct preferences before incapacitation occurs. There are 2 primary types:

• Living will: Expresses preferences for end-of-life care

• Durable power of attorney for health care: Designates a surrogate decision maker

Every state in the US recognizes and has defined these documents by statute to provide a simple legal

tool by which people can express their wishes and have them honored. However, advance directives are not the only means of expressing such wishes. Any authentic expression of patient's wishes should be honored.

An advance directive cannot be completed after a patient becomes mentally incapacitated, and in most states, it does not become effective until after incapacity has been determined. If no advance directive has been prepared, an authorized surrogate (see p. 3469) must be identified or appointed to make health care decisions.

Living will: A living will expresses a patient's preferences for end-of-life health care (it is called a "living" will because it is in effect while the person is still alive). In some states, the document is called a directive to doctors or a declaration. State laws vary greatly regarding scope and applicability of living wills.

A living will allows people to express preferences for the amount and nature of their health care, from no interventions to maximum care. Detailed treatment preferences are desirable because they provide more specific guidance to practitioners. A living will cannot compel health care practitioners to provide health care that is medically or ethically unwarranted.

To be valid, a living will must comply with state law. Some states require that living wills be written in a fairly standardized way. Others are more flexible, permitting any language as long as the document is appropriately signed and witnessed. In most states, a health care practitioner involved in the patient's care cannot be a witness. A document that does not comply with state law requirements for statutory living wills may still serve as a valid communication of a patient's wishes as long as it is an authentic expression of the patient's wishes.

Living wills go into effect upon the loss of ability to make health care decisions or the existence of a medical condition specified in the directive—typically a terminal condition, permanent vegetative state, or the end-stage of a chronic condition. Often, state law provides a process for confirming and documenting the loss of decisional capacity and the medical condition.

Durable power of attorney for health care: In this document, one person (the principal) names another person (the agent, proxy, or the attorney-in-fact) to make decisions about health care and *only* health care. In most states, these documents become legally effective when the principal loses clinical capacity to make health care decisions. Some states recognize *immediately* effective durable powers of attorney for health care, but as a practical matter, the principal retains decision-making authority until incapacity regardless, so there is little practical difference. Like the living will, the durable power of attorney for health care may be referred to by different terms in different states.

While a living will states a person's specific preferences regarding medical treatment, a durable power of attorney for health care designates an agent to make health care decisions. People who have both a living will and a durable power of attorney for health care should stipulate which should be followed if the documents seem to conflict. Because predicting future circumstances in all of their complexity is virtually impossible and because the durable power of attorney for health care designates a decision maker who can respond to here-and-now circumstances, a durable power of attorney is far more practical and flexible than a living will. The agent is granted the power to discuss medical alternatives with the physicians and make decisions if an accident or illness incapacitates the person. In most states, a health care practitioner involved in the care of the patient cannot serve as agent for health care matters, unless the practitioner is a close relative. The durable power of attorney for health care can include a living will provision or any other specific instructions but, preferably, should do so only as guidance for the agent, rather than as a binding instruction.

The durable power of attorney for health care should name an alternate or successor in case the first-named person is unable or unwilling to serve as agent. Two or more people may be named to serve together (jointly) or alone (severally), although reliance on multiple concurrent agents can be problematic. A **jointly held power** requires that all agents agree and act together. In this arrangement, all named agents must be contacted and must agree on every decision. However, this arrangement can be unwieldy because agreement may be difficult to achieve and because one of the agents may be unreachable when a critical decision must be made. A **severally held power** may be more functional because it allows any

named agent to act alone. However, this arrangement can also lead to disagreement, and the courts may eventually have to become involved. For example, if ≥ 2 people serve jointly in severally held power and they absolutely cannot agree, the parties are likely to end up in court.

The use of the durable power of attorney for health care is valuable for adults of all ages. It is especially critical for unmarried couples, same-sex partners, friends, or other individuals who are considered legally unrelated and who wish to grant each other the legal authority to make health care decisions and to ensure rights of visitation and access to medical information.

Ideally, physicians should obtain a copy of a patient's living will and durable power of attorney for health care, review the contents with the patient while the patient is still capable, and make it part of the medical record. A copy of the durable power of attorney for health care should also be given to the patient's appointed agent and another copy placed with important papers. The patient's attorney should hold a copy of all documents. An increasing number of states offer optional electronic registries for recording advance directives.

Do-Not-Resuscitate Orders

The do-not-resuscitate (DNR) order placed in a patient's medical record by a physician informs the medical staff that CPR (see p. 2256) should not be done. This order has been useful in preventing unnecessary and unwanted invasive treatment at the end of life.

Physicians discuss with patients the possibility of cardiopulmonary arrest, describe CPR procedures, and ask patients about treatment preferences. If the patient is incapable of making a decision about CPR, a surrogate may make the decision based on the patient's previously expressed preferences or, if such preferences are unknown, in accordance with the patient's best interests.

Almost all states have specialized DNR protocols for patients who are living at home or in any nonhospital setting. These protocols typically require the signing of an out-of-hospital DNR order by both the physician and patient (or the patient's surrogate) and the use of a special identifier (eg, a bracelet or brightly colored form) that is worn by or kept near the patient. If emergency medical personnel are called in case of emergency and see an intact identifier, they will provide comfort care only and not attempt resuscitation. These protocols are important to know because normally, emergency medical technicians are not expected to read or rely upon a living will or durable power of attorney for health care.

A DNR order does not mean "do not treat." Rather, it means only that CPR will not be done. Other treatments (eg, antibiotic therapy, transfusions, dialysis, use of a ventilator) that may prolong life can still be provided. CPR itself usually does not result in long-term, neurologically intact survival, but other treatments, including aggressive or critical care that prevents cardiac arrest, can. Thus, whether to pursue other treatments is a more important decision than whether to resuscitate. A person with a DNR order can still be treated aggressively in an intensive care unit if their condition warrants.

Medical Malpractice

Patients can sue health care practitioners if they feel they have been injured. However, successful medical malpractice lawsuits require proof of the following:

- The care provided was below the ordinary standard of care that would be provided by similar health care practitioners under similar circumstances.

- A professional relationship existed between the health care practitioner and the injured party.

- The patient was harmed because of the deviation from the standard of care.

Concern about lawsuits sometimes puts pressure on physicians to act in ways that are not necessarily in the best interest of their patients. For example, physicians may order tests or treatments that are not clearly medically necessary just because patients request them or to avoid even a remote possibility of missing something and thus leaving themselves open to a lawsuit. However, such an approach is not

required by law, may not protect against lawsuits, and is generally considered excessive and inappropriate. Also, explaining why a requested test or treatment is not recommended usually satisfies patients. The best defense against malpractice lawsuits is providing excellent health care and building close, trusting, collaborative relationships with patients.

Chapter 352. Financial Issues in Health Care

Introduction

Health care in the US is technologically advanced but expensive, costing about $2.2 trillion dollars in 2007. For decades, health care spending in the US has increased more than the rate of growth for the overall economy; it increased from about 6% of the gross domestic product (GDP) in the 1960s to 16.2% in 2007. The percentage of GDP spent on health care in the US is significantly higher than that in any other nation. The next highest are 11.6% for Switzerland and 11.1% for France; the percentage is 9.8% for Canada and 8.0% for Japan. Also, the amount of money spent per capita on health care in relation to GDP per capita is also higher than that in other countries (see Fig. 352-1). The absolute amount and the rate of increase in the US are widely regarded as unsustainable. Consequently, US health care is currently in flux, as the government attempts to find ways to provide universal health care and reduce its costs.

Consequences of increased US spending on health care include the following:

- Increased government spending (resulting in higher national debt, decreased funding for other programs, or both)
- Slowed growth or a real decline in workers' earnings due to higher payments for health insurance premiums
- Increased costs to employers (resulting in increased product cost and movement of jobs to countries with lower health care costs)
- Increased numbers of people without health insurance (resulting in large increases in un-compensated health care, shifting of cost burden, and poor health outcomes)

Even though US health care spending per capita is the highest in the world, about 46 million people in the US do not have health insurance, whereas other developed countries, despite lower per capita expenditures, ensure universal access to health care. Furthermore, the high spending may not lead to correspondingly superior outcomes; the US ranks comparatively low on many health care outcome measures, such as the following:

- Infant mortality: 30th
- Life expectancy at birth: 23rd for males and 25th for females
- Healthy life expectancy: 24th

Funding

Health care providers in the US are paid by the following:

- Private insurance
- Government insurance programs
- Individual out-of-pocket funds

[**Fig. 352-1.** 2006 health care spending per capita compared to gross domestic product (GDP) per capita.]

In addition, the government directly provides some health care in government hospitals and clinics staffed by government employees. Examples are the Veteran's Health Administration and the Indian Health Service.

Private insurance: Private insurance is purchased from for-profit and not-for-profit insurance

companies, which are accredited separately in each state. Thus, although there are many health insurance companies in the US, a given state tends to have a limited number.

Most private insurance is purchased by corporations as a benefit for employees. Premiums are typically shared by employers and employees. But because the cost of employer-provided health insurance is not considered taxable income for the employee, the government in effect provides some subsidization.

People may also purchase private health insurance themselves. However, unlike in employer-provided policies, applicants for privately purchased policies typically undergo extensive evaluation (underwriting) to identify and reject applicants likely to require costly care, including those with preexisting conditions or a high likelihood of developing disorders. Many applicants are denied policies. Some cannot purchase private insurance at any price. For applicants who do qualify, costs can be much higher for a given policy than when it is purchased through a company or another large group, partly because of administrative costs (often > 30% of the total).

Government insurance programs: The main government insurance programs include

- Medicare (see p. 3155), which funds the elderly, the disabled, and people receiving long-term dialysis therapy

- Medicaid (see p. 3161), which funds certain people living below the poverty level

Other government programs include

- State Children's Health Insurance Program, which provides matching federal funds to states for health insurance for families with children and which was designed to help ensure coverage for uninsured children when family income was below average but too high to qualify for Medicaid

- Tricare, which covers about 9 million active duty and retired military personnel and their families (some Tricare subscribers use government-provided care)

- Veterans Health Administration (VHA), which is a government-operated health care system that provides comprehensive health services to eligible military veterans (about 8 million veterans are enrolled)

- Indian Health Service, which is a system of government hospitals and clinics providing health services to almost 2 million American Indians and Alaskan natives living on or near a reservation

Overall about 30% of the population is covered by government insurance or government-provided care.

Out of pocket: People pay for care not covered by other sources out of their own funds, often using their savings for small expenditures and borrowing (including using credit cards) for large expenditures.

Flexible spending accounts (FSAs) are offered by some employers. Through these accounts, employees can choose to have a limited amount of money deducted from their paychecks to pay for out-of-pocket health care expenses. The money deducted is not subject to federal income taxes. However, the account does not earn interest, and any unused money is forfeited at the end of the year.

Health savings accounts can also be used to pay out-of-pocket expenses; these accounts earn interest, and unused balances need not be forfeited. Most people who are eligible for these accounts are eligible because their health insurance plans limit their reimbursements enough to be classified as high-deductible health plans.

About 17% of health care costs in the US are funded out-of-pocket. Out-of-pocket expenditures for health care contribute significantly to a large number of bankruptcies in the US.

Causes of High Health Care Costs

Health care costs in the US are disproportionately high for many reasons.

Use of costly new technologies and drugs: Such use may be the largest single factor increasing health care costs. Use may be appropriate or inappropriate, but in either case, cost is increased. An example of appropriate but costly treatment is the use of fibrinolysis or angioplasty to treat an MI; before the 1980s, when these treatments began to be used commonly, treating an MI was much less costly (but also less effective). On the other hand, many new and costly treatments, including some in popular use, are ineffective, offer only marginal advantages, or are used inappropriately for patients unlikely to benefit. An example is use of lower lumbar spinal fusion to treat chronic low back pain; many experts think this treatment is ineffective or grossly overused.

Use of many such costly treatments tends to vary considerably among geographic areas and among physician practices within a geographic area (termed practice variation). For some specific disorders (eg, coronary artery disease), health outcomes are no better in areas where adjusted health spending is high than in areas where it is low.

Increased costs of health care goods and services: Drug costs have increased. One reason is the increasing cost of developing a new drug, often in the vicinity of $1 billion. The cost of drug development decreases the economic incentive to develop drugs with lower profit potentials, even those that could substantially benefit particular groups (eg, drugs to treat rare diseases) or public health in general (eg, vaccines, antibiotics).

Marketing of new drugs and devices: Intensive marketing to physicians and consumers (with direct-to-consumer advertising) has been suggested as a cause of overuse of costly new technologies and drugs. Some of these new measures may be no more effective than older, less costly ones.

Overuse of specialty care: Specialists are increasingly providing more care; reasons may include a decreasing number of primary care physicians and an increased desire by patients to see a specialist.

Specialty care is often more expensive than primary care; specialists have higher fees and may do more testing (often pursuing less common diagnoses) than primary care physicians. Also, evaluation and treatment of a patient who could have been managed by a single primary care physician may require more than one specialist.

High administrative costs: The percentage of health care dollars spent on administration is estimated to be 20 to > 30%. Most administrative costs are generated by private insurance, and most of those costs are generated by marketing and underwriting, processes that do not improve medical care. Also, the existence of numerous private insurance plans in the same geographic area typically increases health care providers' costs by making processing (eg, claim submission, coding) complicated and time-consuming.

Physician fees: Physicians in the US are more highly compensated relative to other professionals than physicians in many other countries. This disparity occurs partly because physicians in other countries typically spend far less on their medical education and malpractice insurance than those in the US and have lower office overhead. Because physician fees account for only about 20% of total health care costs, even a significant reduction in physician fees would have only a modest effect on overall costs.

Malpractice costs: The issue of malpractice adds to the cost of medicine directly and indirectly (by triggering defensive medicine).

The direct cost is the malpractice insurance premiums paid by physicians, other providers, health care institutions, and medical drug and device manufacturers. These premiums, which cover claim settlements and malpractice insurance company overhead and profits, must ultimately be paid from health care revenues.

As onerous as premiums and the threat of lawsuits can be for individual physicians (particularly in certain high-risk specialties and geographic areas), the total annual malpractice premium amount paid in 2008 by physicians and institutions was about $12 billion, representing only about 0.6% of total annual health care costs. Actual malpractice settlements paid out in 2008 were $3.6 billion (< 0.2% of health care costs).

Thus, even a major reduction in malpractice settlements would not lower total health care costs significantly, although it could greatly affect certain physicians' practices.

Defensive medicine: Defensive medicine refers to diagnostic or treatment procedures that providers do to guard against the possibility of malpractice litigation, even though such procedures may not be warranted clinically. For example, a physician may hospitalize a patient who is likely to do well with outpatient treatment to avoid a lawsuit in the unlikely event of an adverse outcome.

The actual costs attributable to defensive medicine are difficult to measure. Few rigorous studies have assessed this cost, and estimates from these studies vary greatly, ranging from negligible to substantial (some experts believe that these costs are larger than direct malpractice costs). Some of the uncertainty lies in the fact that defensive medicine is defined subjectively (ie, it is the clinician's reason for doing a test, not how unlikely or uncommon the disorder being tested for is). A clinician's motivation is hard to determine, and different clinicians can reasonably vary in their assessment of the need for testing in a given case (except for a relatively few situations that have clear, sensitive, and specific guidelines for testing). In some survey studies of defensive medicine, physicians were asked whether and when they practice defensive medicine. However, such self-reporting may be unreliable, and such surveys often have a low response rate. Thus, the extent of defensive medicine is unknown.

Furthermore, even when defensive testing can be identified, calculating potential cost savings is not straightforward. Decreasing the amount of defensive testing involves a change in marginal costs (the cost of providing or withholding an additional unit of service), which are different from actual charges or reimbursements. In addition, studies of states that have enacted tort reforms to limit compensation to patients for iatropic injuries have had conflicting results about whether such reforms lower health care expenditures.

Aging of the population: Although often cited as a factor, population aging is probably not responsible for recent increased costs because the generation now in old age has not yet increased disproportionately; also, more effective health care has tended to delay serious illness in this generation. However, the aging of baby boomers may affect costs more as the proportion of the population > 65 increases from about 12% currently to about 20% after 2030.

Containing Health Care Costs

Conceptually, total health care costs can be contained or decreased only by some combination of the following:

• Decreasing use of health care services

• Decreasing reimbursement for services that are used

• Decreasing overhead (payor, provider, or both)

Some strategies adversely affect access to care or outcomes; others may improve care. Evaluating different strategies is difficult, partly because accurately measuring patient-centered health outcomes (eg, morbidity and mortality, quality-adjusted life years [QALY]) tends to be expensive and to require large numbers of patients and long follow-up periods. As a result, most measures used to assess health care quality reflect processes (how care was delivered) rather than outcome. How well these process measures predict ultimate health outcomes is not always clear.

Decreasing Use of Health Care Services

Many strategies can decrease the use of health care services. Many involve limiting access to care (aimed at unnecessary care but sometimes affecting necessary care), but some limit need by improving health.

Limiting access to health care: Traditionally, limiting access has been the strategy used to limit health care costs.

Insurance companies may limit access to care by denying coverage to people likely to need care (eg, those with preexisting conditions) and by dropping coverage of heavy users (rescission).

Government may tighten eligibility criteria for medical assistance programs.

Payors may increase out-of-pocket costs, providing an economic incentive for patients to limit their own health care use. For example, payors may

• Limit the type and number of visits that are reimbursed (eg, mental health care, physical therapy)

• Increase deductibles and co-payments

• Decrease allowable amounts for covered procedures

• Establish or decrease lifetime maximum expenditures

These strategies probably affect outcomes because evidence indicates that many patients avoid necessary as well as unnecessary care. For example, women may avoid screening (eg, Papanicolaou testing, mammography) and subsequently present with late-stage cancer; at-risk patients may avoid influenza vaccination.

By erecting administrative hurdles to care (eg, requiring approval for tests, referrals, and procedures; having complex enrollment procedures and regulations), payors, although not technically denying care, decrease use by a small amount.

State agencies may limit issuance of construction permits for new facilities and laboratories (called certificates of need).

Limiting access to health care can cause problems. For example, when people denied access become seriously ill (which is more likely when routine care is lacking), they are often treated in a hospital on an emergency basis. This care is largely uncompensated (not paid for by patient, insurance, or other source), increasing the burden on people who pay into the health care system, and may be more expensive than if routine care had been provided.

Eliminating unnecessary care: Unnecessary care is easy to define (care that does not improve patient outcome) but often difficult to recognize and still more difficult to eliminate. First steps include conducting more and better studies of comparative effectiveness and cost-effectiveness, so that best practices can be identified. Comparative effectiveness studies can evaluate areas other than drugs, such as effects of exercise, of physical therapy, and of different providers, systems, settings of medical care, and reimbursement systems. Education and monitoring of providers may decrease practice variation and increase cost-effectiveness. Eliminating the economic incentive for providing more intensive care (fee-for-service model) by using prospective payment systems (see below) and pay-for-performance models may encourage providers to eliminate cost-ineffective care processes.

Better coordination of services among providers (eg, by closer communication and use of universally readable electronic medical records) may make evaluation and treatment more efficient (eg, by eliminating duplication of tests).

Encouraging palliative hospice care, when appropriate, may help decrease use of costly, often technology-intensive, cure-directed care.

Improving health: Increased use of relatively inexpensive preventive services (eg, screening, diagnosis, and treatment of diabetes, hypertension, and hyperlipidemia; screening for breast and colon cancer) may decrease the subsequent need for expensive treatments (eg, for MI, stroke, or late-stage cancer). However, preventive measures may not decrease costs for a given private insurance company because savings are often not realized for many years; by that time, many patients have switched insurance plans. In the US, people stay with a given insurance company for an average of about 6 yr (usually determined

by how often they change jobs)—too short to realize a savings via preventive care.

Strategies to increase preventive care include

- Incentives to increase the number of primary care physicians (who can often provide appropriate screening measures and help prevent complications)
- Pay-for-performance measures that financially reward adherence to preventive care guidelines
- Elimination of co-payments for preventive services
- Free preventive services, particularly for needy people

Whether care management programs that attempt to improve patient adherence to treatment plans and clinician adherence to guidelines can improve outcomes or reduce costs (eg, of potentially avoidable hospitalization or complications) is unclear; some studies do not show a benefit.

Decreasing Reimbursement for Care Used

Even when health care is provided, strategies can be used to limit payments.

Lower fees: Payors (government and private) may negotiate lower fees with institutions and providers or simply dictate such fees. In the US, reimbursement rates established by Medicare and Medicaid tend to influence rates paid by other plans, sometimes decreasing reimbursement.

Increased use of primary care: Measures may help increase the use of less costly primary care vs specialty care. For example, in the patient-centered medical home model, primary care practitioners coordinate and integrate all aspects of medical care, including specialty and interdisciplinary care, in various settings (eg, home, hospital, long-term care facility). Many authorities think that this model can decrease unnecessary specialty care, duplicative care, and care that may be inappropriate for the individual's health goals (eg, palliation rather than diagnosis).

Measures to increase the supply of primary care physicians have been proposed. They include increasing reimbursement for primary care, shifting more government funding of residency programs to primary care training, and enhancing the attractiveness of primary care among medical students, although how the last strategy could be implemented is unclear.

Prospective payment systems: In these systems, providers are paid a fixed amount regardless of how much care is provided. The amount may be based on a specified episode of care or be a fixed annual reimbursement per patient. For example, some Medicare reimbursement is based on diagnosis-related groups (DRGs); in such cases, Medicare pays a fixed amount based on the diagnosis. In capitated systems, providers are paid a fixed annual amount to provide health care for patients regardless of the services used.

Prospective payment systems reward less expensive care (and thus usually use of fewer services), in contrast to fee-for-service systems, which reward use of more services. However, prospective payment creates an economic disincentive to care for complex patients (eg, those who have multiple disorders or who are seriously ill) and may inhibit provision of necessary care. Because a decrease in the amount of care provided has the potential to decrease quality of care, quality control systems (eg, professional review organizations) are often also established.

Denial of claims: In the US, unlike in most of the developed world, insurance carriers routinely deny a significant percentage of claims for services delivered to patients. In one study in California, the denial rate averaged about 30% in 2009; some of the claims were paid after appeal, but appealing a claim is quite costly in time and effort for patients, providers, and payors alike.

Competition: Competition among providers for patients and among insurance companies for subscribers is thought to encourage lowering of charges (eg, by those who charge more than their competitors for a

similar service). However, the ultimate consumers (ie, patients) usually do not know providers' charges in advance, and if they know, they often cannot act on this knowledge (eg, because patients are often limited to certain providers and limited in their ability to judge quality of care). Also, because the cost of medical care is subsidized for most consumers (eg, through employer-paid health insurance, tax deductions, and flexible spending accounts or medical savings accounts), consumers have less incentive to price shop than for most other purchases. Thus, competition is most effective in lowering costs and maintaining quality when it is among large organizations. For example, insurance companies can compete for contracts from employers such as corporations or the government; providers such as practitioner organizations and hospitals can compete for contracts with insurance companies.

Competition has some disadvantages. It results in multiple systems of claim submission and evaluation, which require more time from providers, their clerical staff, or both. Also, processes such as eligibility determination, referrals, co-payments, and coding must be coordinated between a large number of incompatible insurance company systems. Thus, competition increases the clerical (administrative) burden of the overall health care system.

Decreased drug costs: Using generic drugs or, when appropriate, more cost-effective brand-name drugs can help decrease drug costs. Strategies include

- Educating providers about cost-effective drug use
- Restricting drug marketing
- Establishing formularies and using pharmacy benefit managers
- Allowing the government to negotiate drug prices for patients covered by government insurance
- Allowing importation of drugs purchased from other countries to the US

Negative effects on medical research: In many academic medical centers, income from clinical practice has enabled physicians and institutions to participate in medical research. Similarly, income from drug sales supports pharmaceutical research. Thus, decreased reimbursement for care and drug sales may cause a decline in medical research. If other sources (eg, government or private grants) are used to fund research, these funds must be considered as health care costs and thus may offset savings realized from decreasing reimbursement.

Decreasing Overhead

Overhead is health care payments that do not go to health care providers (eg, administrative costs, malpractice insurance, corporate profits in for-profit hospitals and insurance companies).

Decreasing payor overhead: Government health care plans in developed countries (including the US) and private health plans outside the US have overhead costs that usually represent 3 to 5% of total costs (ie, ≥ 95% of all health care funds go to the delivery of health care). However, in the US, private insurers have overhead costs of about 20 to 30%, partly because these insurers need staff to do extensive underwriting (identifying and rejecting applicants likely to require costly care, including those with preexisting conditions or a high likelihood of developing disorders), to evaluate claims for denial, and to adjudicate appeals by providers; they also typically need to show a profit. No evidence indicates that these activities and their higher administrative costs improve clinical care or outcomes.

Strategies that may help minimize overhead costs include

- Increased use of standardized electronic health records
- Increased use of government plans and possibly not-for-profit plans, which have lower overhead than for-profit plans

Competition among payors is thought to encourage increased administrative efficiency, but it also

increases the incentives to deny claims and coverage (which itself requires an extensive bureaucracy).

Decreasing provider overhead: Any payor reform that eliminates the need for the many billing and claims personnel who manage the billing of multiple payors and negotiate appeals and justify claims will decrease provider overhead. For example, some countries that have multiple insurance companies vying for business (eg, Germany, Japan) require the following:

• The payment amounts and rules are the same for all insurance companies.

• In many cases, payors are required to pay all provider bills.

• The cost of the same service is the same throughout the country.

Although malpractice costs are a small fraction of overall costs, malpractice costs for certain physicians can consume a considerable part of their annual income. Reforms that significantly decrease the number of suits and settlements should eventually lower premiums and greatly benefit these physicians; such reforms may also decrease the use of unnecessary, defensive medicine.

Chapter 353. The Dying Patient

Introduction

(See also pp. 2755 and 3471.)

The traditional medical approach emphasizes goals such as the following:

• Testing until diagnoses are well-established

• Correcting all physiologic abnormalities, even asymptomatic ones

• Pursuing a cure, even when cure is unlikely and therapy is toxic, invasive, or uncomfortable

However, to many patients facing a fatal illness, these goals may be less important than avoiding suffering and (with their family and friends) finding comfort and meaningfulness during the experience of dying. Thus, care of the dying patient should be guided by a realistic assessment of the situation and the merits of various interventions in light of the patient's values and wishes.

People's priorities differ, especially when facing death. Some prefer life to be prolonged, even at the cost of pain, marked confusion, or severe respiratory distress. They may cherish every moment of life, regardless of its quality. For others, quality of life is the overarching concern. They may fear pain or confusion more than death and prefer comfort measures and shorter survival to prolonged disability and struggle. However, to say that a patient's care has changed from curative to supportive or from treatment to palliation is an oversimplification of a complex decision process. Most patients need a customized mix of treatment to correct, prevent, and mitigate the effects of various illnesses and disabilities.

Some people search for closure: They reach out to friends and family to share time and to express love; they complete projects important to their lives and tie up loose ends. Often, with appropriate support, people die at a time and in a way that allows them to experience a satisfying close. Other people cannot accept their imminent mortality and avoid such closure.

Effective care for dying patients usually involves a clinical team because no one caregiver is available 24 h/day and because comprehensive, reliable care requires the skills and perspectives of several disciplines. Palliative care or hospice teams anticipate potential problems and make appropriate arrangements, such as obtaining supplies or opioids in anticipation of a potential emergency. Certain team members can help dying patients who have spiritual needs; such needs should be recognized, acknowledged, and addressed. When death is imminent, an experienced team member can comfort family members and may prevent an inappropriate call to the emergency medical system.

When Death Is Near

The physician and the clinical team should prepare patients and family members for death whenever patients have a condition likely to worsen and cause death, even if death may be a few years in the future. Preparation includes discussion of the likely course and possible complications. Patients should also be advised when death becomes imminent. A health care practitioner must not assume that patients or family members understand the fatal nature of certain disorders (even metastatic cancer) or that they can recognize from a patient's appearance that death is near. Initial discussions should be honest and sensitive to the language and culture of patients and family members. The physician should not delay full disclosure too long because doing so can provide false hope and distort decision making—for example, by reducing the opportunity to attend to spiritual and family concerns. Many patients and family members benefit from making plans based on their priorities and preferences for end-of-life treatments (see p. 3471).

Many patients ask whether the clinician can predict the time until death. Such estimates are ordinarily incorrect, both for slowly progressive disorders and for disorders in which death tends to come suddenly, without reliable warning signs (eg, heart failure, emphysema). For some cancers, recognizable warning signs may presage death by several weeks or months. In contrast, many people live for months or years

in an unchanging but very fragile state of health. Clinicians tend to give inaccurately optimistic estimates and often are reluctant to predict life expectancy. Some models, such as the Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) used to predict in-hospital mortality for ICU patients, are accurate for groups but not for individuals. If a clinician notes that a patient is sick enough that it would be "no surprise" for the patient to die in the coming year, the patient could die with the next complication, which could develop at any time. In such cases, clinicians, patients, and family members should consider prioritizing comfort and life closure over at least the burdensome elements in conventional medical treatment, as well as many preventive services. Family support, advance care planning, focus on relieving symptoms and maximizing function, and attention to spiritual issues are appropriate for patients who are in such fragile health. Clinicians lose many opportunities to help patients and their families live well and meaningfully by postponing the recognition of fragile health until death is clearly imminent.

At some point, virtually every dying patient should have a do-not-resuscitate (DNR) order or a do-not-attempt-resuscitation (DNAR) order written in the medical record. All clinicians in every setting should abide by that decision. Patients, family members, and the clinical team should also make and record other important decisions about medical care (eg, whether patients are to be hospitalized or use a ventilator). Often, implementing these decisions requires specific actions (eg, to have the needed drugs at home).

Family members should know about the changes that may occur in the patient's body shortly before and after death. They should not be surprised by irregular breathing, cool extremities, confusion, a purplish skin color, or somnolence in the last hours.

Some patients close to death develop noisy bronchial congestion or palatal relaxation, commonly known as the death rattle. If this symptom distresses family members, scopolamine or diphenhydramine (see p. 3485) can dry the patient's secretions and reduce the noise. Also, CNS irritability, with agitation and restlessness, may develop. If these symptoms, after review, are judged not to be caused by a drug or untreated disorder, they can be relieved by a sedative.

If a patient is expected to die at home, family members should rehearse whom to call (eg, physician, hospice nurse, clergy) and know whom not to call (eg, ambulance service, 911). They should also have help in obtaining legal advice and arranging burial or cremation services. Religious practices that may affect after-death care of the body should be discussed before death with the patient, family members, or both.

The last moments of a patient's life can have a lasting effect on family members, friends, and caregivers. The patient should be in an area that is peaceful, quiet, and physically comfortable. Any stains or tubes on the bed should be covered, and odors should be masked. Family members should be encouraged to maintain physical contact, such as holding hands, with the patient. If desired by the patient and family members, the presence of friends and clergy should be encouraged. Accommodation should be made for spiritual, cultural, ethnic, or personal rites of passage desired by the patient and family members.

When resuscitation is attempted, family members often appreciate being present during the resuscitation.

After Death Occurs

A physician, nurse, or other authorized person should pronounce the patient dead in a timely way to reduce the family's anxiety and uncertainty. The physician should complete the death certificate as soon as possible because funeral directors need a completed death certificate to make final arrangements. Even when death is expected, physicians may need to report the death to the coroner or police; knowledge of local law is important.

Telling family members about death, particularly unexpected death, requires effort. The physician should use clear language when informing the family that death has occurred (eg, using the word "died"). Euphemisms (eg, "passed on") should not be used because they are easily misinterpreted. If the family was not present during resuscitation, any events near death, including resuscitative efforts, should be described and the patient's absence of pain and distress mentioned (if true). It is usually wise to be sure that the closest kin is not alone. When told about death, particularly unexpected death, family members

may be overwhelmed and unable to process information given to them or to formulate questions. Physicians, nurses, and other health care practitioners should respond to the psychologic needs of family members and provide appropriate counseling, a comfortable environment where family members can grieve together, and adequate time for them to be with the body. When feasible, it may help for a clinician to be with the family members as they enter the room with a newly dead body because that situation is so unfamiliar to most people. Sometimes it is best then to leave family members alone for a while, then return and offer explanations of treatments provided and give the family a chance to ask questions. Friends, neighbors, and clergy may be able to help provide support. Health care practitioners should be sensitive to cultural differences in behavior at the time of death.

The patient or family members and the clinical care team should discuss organ and tissue donation, if appropriate, before death or immediately after death; such discussions are ordinarily mandated by law. The attending physician should know how to arrange for organ donation and autopsy, even for patients who die at home or in a nursing home. Autopsy should be readily available regardless of where the death occurred, and decisions about autopsies can be made before death or just after death. A substantial minority of families welcome an autopsy to clear up uncertainties, and clinicians should appreciate the role of autopsy in quality assessment and improvement.

Hospice Care

• Emphasis on symptom relief and comfort care

• Decreased emphasis on prolonging life

• Little diagnostic testing

Hospice is a concept and program of care that is specifically designed to minimize suffering for dying patients and their family members. In the US, hospice is the only widely available comprehensive program to support very sick people at home. Philosophically, hospice programs forgo most diagnostic testing and life-prolonging treatments in favor of symptom relief, education of patients and family members about appropriate care, and comfort care.

Hospice is always interdisciplinary, relying on a core team of physicians, nurses, social workers, and attendants (eg, home health aides). Pharmacists, nutritionists, and therapists may also be involved. Hospice program personnel care for patients at home, in nursing homes, or in other care facilities. Although hospice program personnel do not usually care for patients in hospitals and rehabilitation centers, many hospitals are establishing palliative care programs to address the same care issues.

Hospice programs differ substantially in the services they provide and in treatments and devices they use. Whether a particular patient and family should participate in a given program depends on their needs and wishes, on their financial considerations, and on the skills and capacity of the local programs.

Hospice care can provide most necessary medical treatments. Nurses ordinarily oversee and implement the general plan of care, including drug use, O_2 therapy, and IV lines or other special equipment. Nurses are usually the first ones to assess and address patient needs. They can usually adjust drug doses and help obtain any new drugs or treatments. Hospice physicians see patients when needed and share in shaping the plan of care. Social workers, chaplains, and volunteers help with interpersonal, spiritual, and financial issues. Bereavement counselors support survivors through the grieving process. Hospice plans of care help family members prepare for the challenges of facing the death of a loved one and dealing with the situation at the time of death, including their role and how to obtain needed help.

Most patients ill enough to require hospice also require some assistance with daily activities (eg, dressing, bathing, preparing food), and some may be completely dependent. Family members and friends often provide this care, but additional help from home health aides and volunteers may be necessary.

Medicare or insurance mostly pays a per diem rate that is intended to cover all hospice services, including a negotiated amount of help from home health aides, but only after a physician certifies that the patient has a fatal disorder with life expectancy < 6 mo.

Physicians may be reluctant to use hospice because a treatable condition could develop. However, this reluctance is not justified because many treatable conditions are within the scope of hospice care, and patients can leave hospice at any time and re-enroll later.

Other Concerns

Patient, family members, and clinicians should consider the following:

• They should plan for increasing disability.

• Obtaining payment for end-of-life care may be difficult.

• Emphasis should be on improving quality of end-of-life, not on hastening death.

Managing disability: Progressive disability often accompanies fatal illnesses. Patients may gradually become unable to tend to a house or an apartment, prepare food, handle financial matters, walk, or care for themselves. Most dying patients need help during their last weeks. Disability should be anticipated and appropriate preparations made (eg, choosing housing that is wheelchair-accessible and close to family caregivers). Services such as occupational or physical therapy and hospice care may help a patient remain at home, even when the disability progresses.

Financial concerns: Financial coverage for care of dying patients is problematic. Medicare regulations restrict payment for many aspects of supportive care. Not all patients qualify for hospice care, and physicians are often reluctant to certify the 6-mo prognosis required for hospice coverage. Sometimes the need for skilled nursing care can justify Medicare payment to a nursing home for short-term, complex medical and nursing needs for dying patients. One study has shown that one third of families deplete most of their savings when caring for a dying relative. The clinical care team should know the financial effects of choices and discuss these issues with patients or family members. Some attorneys specialize in elder care and can help patients and their family members deal with these issues.

Legal and ethical concerns: Health care practitioners should know local laws and institutional policy governing living wills, durable powers of attorney, and procedures for forgoing resuscitation and hospitalization. This knowledge helps them ensure that the patient's wishes guide care, even when the patient can no longer make decisions (see p. 3468).

Many health care practitioners worry that medical treatments intended to relieve pain or other suffering can hasten death, but this effect is actually quite uncommon. With thoughtful and skillful medical care, accusations of assisted suicide or other wrongdoing are almost nonexistent. Even if dyspnea requires doses of opioids that may also hasten death, the resulting death is not considered wrongful.

However, actually assisting with suicide (eg, by directly providing a dying patient with lethal drugs and instructions for using them) could be grounds for prosecution in most states but is authorized under specific conditions in Oregon. Charges of homicide are plausible if the patient's interests are not carefully advocated, if the patient lacks capacity or is severely functionally impaired when decisions are made, if decisions and their rationales are not documented, or if the prosecutor's electoral base is expected to approve of such charges. Physicians who manage symptoms vigorously and forgo life-sustaining treatment need to document decision making carefully, provide care in a reputable setting, and discuss these issues willingly, honestly, and sensitively with patients, other practitioners, and the public. A physician should not provide an intervention that is conventionally considered a means of homicide (eg, lethal injection) even if the intention is to relieve suffering.

Symptom Control in the Dying

Patients need reassurance that symptoms will not be overwhelming.

Physical and mental distress is common while living with fatal illness, but much distress can be prevented or relieved. Patients commonly fear protracted and unrelieved suffering. Knowing they can count on living

reasonably comfortably enables patients to focus on living as fully as possible and on confronting the issues presented by fragile health and the approach of death.

Symptom control should be based on etiology when possible. For example, vomiting due to hypercalcemia requires different treatment from that due to elevated intracranial pressure. However, diagnosing the cause of a symptom may be inappropriate if testing is burdensome or risky or if specific treatment (eg, major surgery) has already been ruled out. For dying patients, comfort measures, including nonspecific treatment or a short sequential trial of empiric treatments, are often better than an exhaustive diagnostic evaluation.

Because one symptom can have many causes and may respond differently to treatment as the patient's condition deteriorates, the clinical team must monitor and reevaluate the situation frequently. Drug overdosage or under-dosage is harmful, and both become more likely as worsening physiology causes changes in drug disposition.

When survival is likely to be brief, symptom severity frequently dictates initial treatment. Sometimes the fear that a symptom will worsen can be more crippling than the symptom itself, and reassurance that effective treatment is available may be all a patient needs. When a symptom is quite severe or the diagnostic alternatives do not affect treatment, the physician should quickly relieve suffering by treating the symptom.

Pain

About half of patients dying of cancer have severe pain. Yet, only half of these patients receive reliable pain relief. Many patients dying of organ system failure and dementia also have severe pain. Sometimes pain can be controlled but persists because patients, family members, and physicians have misconceptions about pain and the drugs (especially opioids) that can control it, resulting in significant underdosing.

Patients perceive pain differently, depending partly on whether other factors (eg, fatigue, insomnia, anxiety, depression, nausea) are present. Analgesic choice depends largely on pain intensity and cause, which can be determined only by talking with and observing patients. Patients and physicians must recognize that all pain can be relieved by an appropriately potent drug at sufficient dosage, although aggressive treatment may also cause sedation or confusion. Commonly used drugs are aspirin, acetaminophen, or NSAIDs for mild pain; oxycodone for moderate pain; and hydromorphone, morphine, or fentanyl for severe pain (see p. 1623).

In dying patients, oral opioid therapy is most convenient and cost-effective. Rectal opioid therapy provides more uneven absorption; however, 1st-pass effect is often minimal. Morphine suppositories or pills may be given rectally at the same dosage used for oral forms and then titrated as needed. IV or sc opioid therapy is better than IM injections, which are painful and result in variable absorption. Long-acting opioids are best for long-lasting pain. When giving opioids, the physician should prescribe them in adequate dosage and on a continuous basis to prevent pain. Unreasonable concerns by the public and by health care practitioners about addiction often tragically limit appropriate use of opioids. Pharmacologic dependence may result from regular use but causes no problems in dying patients except the need to avoid inadvertent withdrawal. Addictive behaviors are rare and usually easy to control.

Adverse effects of opioids include nausea, sedation, confusion, constipation, and respiratory depression. Constipation should be treated prophylactically (see p. 3486). Patients usually develop substantial tolerance to the respiratory depressant and sedative effects of morphine but have much less tolerance for the analgesic and constipating effects. Opioids may also cause myoclonus, agitated delirium, hyperalgesia, and seizures. These effects may result from accumulation of toxic metabolites and usually resolve when another opioid is substituted. Patients with these adverse effects and serious pain often warrant consultation with a palliative care specialist or pain specialist.

When a stable opioid dose becomes inadequate, increasing the dose by 1 1/2 to 2 times the previous dose is reasonable. Usually, serious respiratory depression does not occur unless the new dose is much more than twice the previously tolerated dose. Clinicians often are unfamiliar and thus uncomfortable with

such large dosage increases. Increasing the dose over 1 to 2 h with constant observation and having opioid antagonists immediately available can overcome that reluctance.

Use of adjunctive drugs for pain control often increases comfort and reduces the opioid dosage and consequent adverse effects. Corticosteroids can reduce the pain of inflammation and swelling. Tricyclic antidepressants (eg, nortriptyline, doxepin) help manage neuropathic pain (see p. 1632); doxepin can provide bedtime sedation as well. Gabapentin 300 to 1200 mg po tid helps relieve neuropathic pain. Methadone is effective for refractory or neuropathic pain; however, its kinetics vary and it requires close monitoring. Benzodiazepines are useful for patients whose pain is worsened by anxiety.

For severe localized pain, regional nerve blocks given by an anesthesiologist experienced in pain management may provide relief with few adverse effects. Various nerve-blocking techniques may be used. Indwelling epidural or intrathecal catheters can provide continuous infusion of analgesics, often mixed with anesthetic drugs.

Pain-modification techniques (eg, guided mental imagery, hypnosis, acupuncture, relaxation, biofeedback) help some patients (see p. 3417). Counseling for stress and anxiety may be very helpful, as may spiritual support from a chaplain.

Dyspnea

Dyspnea is one of the most feared symptoms and is extremely frightening to dying patients.

Quickly reversible causes should be treated specifically. For example, placing a chest tube for tension pneumothorax or doing thoracentesis for a pleural effusion provides quick and definitive relief. However, if death is imminent or a definitive treatment for the cause of dyspnea is not available, proper symptomatic treatment assures patients they will be comfortable, regardless of the cause.

As a first intervention, O_2 helps correct hypoxemia. Even when its oxygenating benefit is no longer certain, O_2 may continue to be psychologically comforting to patients and family members. O_2 therapy is most comfortable by nasal cannula, so this route is preferred unless higher concentrations are critically important.

Morphine 2 to 10 mg sublingually or 2 to 4 mg sc q 2 to 4 h prn helps reduce breathlessness in an opioid-naive patient. Such a low dosage of morphine may blunt the medullary response to CO_2 retention or O_2 decline, reducing dyspnea and decreasing anxiety without causing harmful respiratory depression. If patients are already taking opioids for pain, dosages that relieve dyspnea must often be more than double the patient's usual dosages.

Airway congestion is best managed with drugs that dry secretions (eg, topical scopolamine gel 0.25 to 0.5 mg q 8 to 12 h applied to the skin behind the ear or on the chest, hyoscyamine 0.125 mg sublingually q 8 h, diphenhydramine 10 to 50 mg IM q 4 to 6 h prn).

Nebulized saline may help patients with viscous secretions. Nebulized albuterol and oral or injectable corticosteroids may relieve bronchospasm and bronchial inflammation.

Benzodiazepines often help relieve anxiety associated with dyspnea and with the fear of a return of dyspnea. Useful nondrug measures include providing a cool draft from an open window or fan and maintaining a calming presence.

Anorexia

Anorexia and marked weight loss are common among dying patients. For family members, accepting the patient's poor oral intake is often difficult because it means accepting that the patient is dying. Patients should be offered their favorite foods whenever possible. Conditions that may cause poor intake and that can be easily treated—gastritis, constipation, toothache, oral candidiasis, pain, and nausea—should be treated. Some patients benefit from appetite stimulants such as oral corticosteroids (dexamethasone 2 to

8 mg bid or prednisone 10 to 30 mg once/day) or megestrol 160 to 480 mg po once/day. However, if a patient is close to death, family members should understand that neither food nor hydration is necessary to maintain the patient's comfort.

IV fluids, TPN, and tube feedings do not prolong the life of dying patients. All of these measures seem to increase discomfort and may hasten death. Pulmonary congestion and pneumonia are more common among dying patients who are fed artificially. Artificial hydration may worsen edema and pain associated with inflammation. Conversely, dehydration and ketosis due to caloric restriction correlate with analgesic effects and absence of discomfort. The only reported discomfort due to dehydration near death is xerostomia, which is easily relieved with oral swabs or ice chips.

Family members should be gently told that the patient is dying and that food does not help the patient's strength nor substantially delay death; they should be reassured that the patient does not suffer from having little or no intake. Having family members and friends take on specific tasks (eg, providing favorite foods, small portions, and foods that are easy to swallow) provides other ways to show caring and love, which can help family members.

Even debilitated and cachectic patients may live for several weeks with no food and minimal hydration. Family members should understand that stopping fluids does not result in the patient's immediate death and ordinarily does not hasten death. Supportive care, including good oral hygiene, is imperative for patient comfort during this time.

Nausea and Vomiting

Many seriously ill patients experience nausea, frequently without vomiting. Nausea may arise with GI problems (eg, constipation, gastritis), metabolic abnormalities (eg, hypercalcemia, uremia), drug adverse effects, increased intracranial pressure secondary to cerebral cancer, and psychosocial stress. When possible, treatment should match the likely cause—eg, stopping NSAIDs, treating gastritis with H_2 blockers, and trying corticosteroids for patients with known or suspected brain metastases. If nausea is due to gastric distention and reflux, metoclopramide (eg, 10 to 20 mg po or sc qid prn or given on a scheduled basis) is useful because it increases gastric tone and contractions while relaxing the pyloric sphincter.

Patients with no specific cause of nausea may benefit from treatment with a phenothiazine (eg, promethazine 25 mg po qid; prochlorperazine 10 mg po before meals or, for patients who cannot take oral drugs, 25 mg rectally bid). Anticholinergic drugs such as scopolamine and the antihistamines meclizine and diphenhydramine prevent recurrent nausea in many patients. Combining lower doses of the previously mentioned drugs often improves efficacy. Second-line drugs for intractable nausea include haloperidol (started at 1 mg po or sc q 6 to 8 h, then titrated to as much as 15 mg/day). The 5-HT_3 antagonists ondansetron and granisetron often dramatically relieve chemotherapy-induced nausea. Cost often makes these antagonists 2nd-line drugs for more complex causes of nausea in dying patients.

Nausea and pain due to intestinal obstruction are common among patients with widespread abdominal cancer. Generally, IV fluids and nasogastric suction are more burdensome than useful. Symptoms of nausea, pain, and intestinal spasm respond to hyoscyamine (0.125 to 0.25 mg q 4 h sublingually or sc), scopolamine (1.5 mg topically), morphine (given sc or rectally), or any of the other previously mentioned antiemetics. Octreotide 150 µg sc or IV q 12 h inhibits GI secretions and dramatically reduces nausea and painful distention. Given with antiemetics, octreotide usually eliminates the need for nasogastric suctioning. Corticosteroids (eg, dexamethasone 4 to 6 mg IV, IM, or rectally tid) may decrease obstructive inflammation at the tumor site and temporarily relieve the obstruction. IV fluids may exacerbate obstructive edema.

Constipation

Constipation is common among dying patients because of inactivity, use of opioids and drugs with anticholinergic effects, and decreased intake of fluids and dietary fiber. Regular bowel movements are essential to the comfort of dying patients, at least until the last day or two of life. Laxatives help prevent fecal impaction, especially in patients receiving opioids. Monitoring bowel function regularly is essential.

Most patients do well on a twice/day regimen of stool softener (eg, docusate) plus a mild stimulant laxative (eg, casanthranol, senna). If stimulant laxatives cause cramping discomfort, patients may respond to increased doses of docusate alone or an osmotic laxative, such as lactulose or sorbitol started at 15 to 30 mL po bid and titrated to effect.

Soft fecal impaction may be treated with a bisacodyl suppository or saline enema. For a hard fecal impaction, a mineral oil enema may be given, possibly with an oral benzodiazepine (eg, lorazepam) or an analgesic, followed by digital disimpaction. After disimpaction, patients should be placed on a more aggressive bowel regimen to avoid recurrence.

Pressure Ulcers

Many dying patients are immobile, poorly nourished, incontinent, and cachectic and thus are at risk of pressure ulcers (see also p. 736). Prevention requires relieving pressure by rotating the patient or shifting the patient's weight every 2 h; a specialized mattress or continuously inflated air-suspension bed may also help. Incontinent patients should be kept as dry as possible. Generally, use of an indwelling catheter, with its inconvenience and risk of infection, is justified only when bedding changes cause pain or when patients or family members strongly prefer it.

Confusion

Mental changes that can accompany the terminal stage of a disorder may distress patients and family members; however, patients are often unaware of them. Confusion (delirium) is common; causes include drugs, hypoxia, metabolic disturbances, and intrinsic CNS disorders. If the cause can be determined, simple treatment may enable patients to communicate more meaningfully with family members and friends. Patients who are comfortable and less aware of their surroundings may do better with no treatment. When possible, the physician should ascertain the preferences of patients and family members and use them to guide treatment.

Simple causes of confusion and agitation should be sought. Agitation and restlessness often result from urinary retention, which resolves promptly with urinary catheterization. Confusion in debilitated patients is worsened by sleep deprivation. Agitated patients may benefit from benzodiazepines; however, benzodiazepines may also cause confusion. Poorly controlled pain may cause insomnia or agitation. If pain has been appropriately controlled, a nighttime sedative may help.

Family members and visitors may help lessen confusion by frequently holding the patient's hand and repeating where the patient is and what is happening. Patients with severe terminal agitation resistant to other measures may respond best to barbiturates; family members should be made aware that when near death, patients do not usually wake up much after starting these drugs. Pentobarbital, a rapid-onset, short-acting barbiturate, may be given as 100 to 200 mg IM q 4 h prn. Phenobarbital, which is longer-acting, may be given po, sc, or rectally. Midazolam, a short-acting benzodiazepine, also is often effective.

Depression

Most dying patients experience some depressive symptoms. Providing psychologic support and allowing patients to express concerns and feelings are usually the best approach. A skilled social worker, physician, nurse, or chaplain can help with these concerns.

A trial of antidepressants is often appropriate for patients who have persistent, clinically significant depression. SSRIs are useful for patients likely to live beyond the 4 wk usually needed for onset of the antidepressant effect. Depressed patients with anxiety and insomnia may benefit from a sedating tricyclic antidepressant given at bedtime. For patients who are withdrawn or who have vegetative signs (see p. 1666), methylphenidate may be started at 2.5 mg po once/day and increased to 2.5 to 5 mg bid (given at breakfast and lunch) as necessary. Methylphenidate (same dosage) can provide a few days or weeks of increased energy for patients who are fatigued or somnolent because of analgesics. Methylphenidate has a rapid effect but may precipitate agitation. Although its duration of action is short, adverse effects are also short-lived.

Stress

A few people approach death peacefully, but more patients and family members experience stressful periods. Death is particularly stressful when interpersonal conflicts keep patients and family members from sharing their last moments together in peace. Such conflicts can lead to excessive guilt or inability to grieve in survivors and can cause anguish in patients. A family member who is caring for a dying relative at home may experience physical and emotional stress. Usually, stress in patients and family members responds to compassion, information, counseling, and sometimes brief psychotherapy. Community services may be available to help relieve care-giver burden. Sedatives should be used sparingly and briefly.

When a partner dies, the survivor may be overwhelmed by having to make decisions about legal or financial matters or household management. For an elderly couple, the death of one may reveal the survivor's cognitive impairment, for which the deceased partner had compensated. The clinical team should identify such high-risk situations so that they can mobilize the resources needed to prevent undue suffering and dysfunction.

Grief

Grieving is a normal process that usually begins before an anticipated death. For patients, grief often starts with denial caused by fears about loss of control, separation, suffering, an uncertain future, and loss of self. Traditionally, the stages after grief were thought to occur in the following order: denial, anger, bargaining, depression, and acceptance. However, the stages that patients go through and their order of occurrence vary. Members of the clinical team can help patients accept their prognosis by listening to their concerns, helping them understand that they can control important elements of their life, explaining how the disorder will worsen and how death will come, and assuring them that their physical symptoms will be controlled. If grief is still very severe or causes psychosis or suicidal ideation or if the patient has a previous severe mental disorder, referral for professional evaluation and grief counseling may be needed.

Family members may need support in expressing grief. Any clinical team member who has come to know the patient and family members can help them through this process and direct them to professional services if needed. Physicians and other clinical team members need to develop regular procedures that ensure follow-up of grieving family members.