

**Box 9-2****TNM STAGING SYSTEM**

<b>T: Primary Tumor</b>	
TX	Primary tumor cannot be assessed
T <sub>0</sub>	No evidence of primary tumor
T <sub>IS</sub>	Carcinoma in situ (confined to site of origin)
T <sub>1</sub> , T <sub>2</sub> , T <sub>3</sub> , T <sub>4</sub>	Progressive increase in tumor size and involvement locally
<b>N: Regional Lymph Nodes</b>	
N <sub>x</sub>	Nodes cannot be assessed
N <sub>0</sub>	No metastasis to regional lymph nodes
N <sub>1</sub> , N <sub>2</sub> , N <sub>3</sub>	Increasing degrees of involvement of regional lymph nodes
<b>M: Distant Metastasis</b>	
M <sub>x</sub>	Presence of distant metastasis cannot be assessed
M <sub>0</sub>	No distant metastasis
M <sub>1</sub>	Distant metastasis

Note: Extension of primary tumor directly into lymph nodes is considered metastasis to lymph nodes. Metastasis to a lymph node beyond the regional ones is considered distant metastasis.

can lead to misstaging and delayed diagnosis and treatment. Staging continues to improve with new, more precise levels of screening sensitivity. For example, molecular screening for the presence of markers characteristic of some diseases nearly eliminates the possibility of true disease stage.<sup>203</sup>

### Grading

Grading 1 through 4 is another way to define a tumor and classifies the degree of malignancy and differentiation of malignant cells. For example, a low-grade tumor typically has cells more closely resembling normal cells and tends to remain localized, whereas a high-grade tumor has poorly differentiated cells that tend to metastasize early. Staging is more predictive than grading.

## INCIDENCE

Estimates of worldwide incidence, mortality, and prevalence of 26 cancers are available from the International Agency for Research on Cancer (IARC). Geographic variations between 20 large areas of the world are presented. Most of the international variation is due to exposure to known or suspected risk factors related to lifestyle or environment. The IARC has been researching and providing a database of global cancer estimates (GLOBOCAN) for the last 30 years.<sup>55</sup>

The most commonly diagnosed cancers are lung, breast, and colorectal; the most prevalent cancer in the world is breast cancer (4.4 million survivors up to 5 years after diagnosis). Lung cancer accounts for the most number of cancer deaths worldwide.<sup>143</sup> The ACS publishes annual cancer statistics and estimates cancer trends (Fig. 9-1). Each year the ACS calculates estimates of the number of new cancer cases and expected cancer deaths in the United States and compiles the most recent data on cancer incidence, mortality, and survival.<sup>96</sup>

Based on statistical estimates, in the year 2007, the ACS predicts about 1.4 million new cases of invasive cancer in the United States and approximately 565,000 cancer-related deaths. This figure does not include most skin cancers, which are expected to affect 1 million people per year.<sup>96</sup>

It is estimated that at least one in three people will be diagnosed with some form of invasive cancer in their lifetime and 3 of 5 people will be cured and/or survive 5 years after cancer treatment. However, cancer is still the second leading cause of death in the United States, exceeded only by heart disease. Poor health and nutrition habits, continued smoking, ozone destruction, and a long-term lack of exercise among many people continue to be discussed as contributors to the overall rise of this disease.<sup>178</sup>

The National Cancer Institute (NCI) established the Surveillance, Epidemiology, and End Results (SEER) program in 1973 as a way to report population-based data of site-specific incidences and outcomes of cancer. Because the United States does not have a nationwide cancer registry, the precise number of new cases of cancer diagnosed each year in the United States is not fully known. As a result of this, the number of new cancer cases occurring annually is estimated using complex statistical measures.<sup>157</sup>

## Trends in Cancer Incidence and Survival

Overall incidence of cancer peaked in 1990 and has declined in the last decade by an average of 1.1% annually, with a 1.4% decline in cancer death rates. In 2003 and 2004, the rate doubled to 2% per year, largely attributed to smoking cessation among men, which peaked in the mid 1960s. The latest drop in cancer deaths occurred across all four major cancer types (lung, colon and rectal, prostate, and breast; lung cancer deaths in women stayed relatively constant).

Survival rates for cancer are on the rise, increasing from 50% to 64% over the last 30 years. There are nearly 10 million cancer survivors in the United States today. Targeted cancer therapies promise to improve these statistics in the coming years. Cancer prevention strategies may reduce the incidence of cancer occurrence and recurrence.<sup>82</sup>

## Gender-Based Incidence

Among men, the most common cancers are predicted to be cancers of the prostate, lung and bronchus, and colon/rectum. Among women, the three most commonly diagnosed cancers are expected to be cancers of the breast, lung and bronchus, and colon/rectum.

The largest decreases in deaths occurred among men (especially among black men) who bear the heaviest overall cancer burden and colorectal cancer in particular. Officials have attributed the steady downward trends to improved vigilance among Americans, who are benefiting from early screening and advances in treatment, as well as smoking less, improving their diets, and exercising more.

**Estimated New Cases\***

			Males	Females		
Prostate	186,320	25%			Breast	182,460 26%
Lung and bronchus	114,690	15%			Lung and bronchus	100,330 14%
Colon and rectum	77,250	10%			Colon and rectum	71,560 10%
Urinary bladder	51,230	7%			Uterine corpus	40,100 6%
Non-Hodgkin lymphoma	35,450	5%			Non-Hodgkin lymphoma	30,670 4%
Melanoma of the skin	34,950	5%			Thyroid	28,410 4%
Kidney and renal pelvis	33,130	4%			Melanoma of the skin	27,530 4%
Oral cavity and pharynx	25,310	3%			Ovary	21,650 3%
Leukemia	25,180	3%			Kidney and renal pelvis	21,260 3%
Pancreas	18,770	3%			Leukemia	19,090 3%
All sites	745,180	100%			All sites	692,000 100%

**Estimated Deaths**

			Males	Females		
Lung and bronchus	90,810	31%			Lung and bronchus	71,030 26%
Prostate	28,660	10%			Breast	40,480 15%
Colon and rectum	24,260	8%			Colon and rectum	25,700 9%
Pancreas	17,500	6%			Pancreas	16,790 6%
Liver and intrahepatic bile duct	12,570	4%			Ovary	15,520 6%
Leukemia	12,460	4%			Non-Hodgkin lymphoma	9,370 3%
Esophagus	11,250	4%			Leukemia	9,250 3%
Urinary bladder	9,950	3%			Uterine corpus	7,470 3%
Non-Hodgkin lymphoma	9,790	3%			Liver and intrahepatic bile duct	5,840 2%
Kidney and renal pelvis	8,100	3%			Brain and other nervous system	5,650 2%
All sites	294,120	100%			All sites	271,530 100%

**Figure 9-1**

Estimated new cancer cases (top) and cancer deaths (bottom), 2008, in the United States (percent distribution of sites by gender). (From Jemal A, Siegel R, Ward E, et al: Cancer statistics, 2008, CA Cancer J Clin 58[2]:71-91, 2008.)

The decline in rates of breast cancer deaths has been attributed in part to increased mammography but also to more aggressive therapy; overall decline in deaths among women may also be the result of the recent falloff in hormone replacement therapy.

Although death rates from breast cancer continue to decline, the incidence of the disease climbed 1.2% annually between 1992 and 2000. Breast cancer alone accounted for approximately 178,400 new cancer cases in women in 2007.<sup>96</sup>

Likewise, improved screening, detection, and treatment of prostate cancer have resulted in a decline in the death rate associated with this type of cancer. About a dozen cancers continue to rise in incidence or mortality, including melanoma, non-Hodgkin's lymphoma, thyroid, esophageal cancer, breast (increased incidence but decreased mortality), and female lung cancer.

**ETIOLOGY**

The cause of cancer varies, and causative agents are generally subdivided into two categories: those of endogenous (genetic) origin and those of exogenous (environmental or external) origin. It is likely that most cancers develop as a result of multiple environmental, viral, and genetic factors working together to disrupt the immune system along with failure of an aging immune system to recognize and scavenge cells that have become less differentiated.

Certain cancers show a familial pattern, giving people a hereditary predisposition to cancer. The most common cancers showing a familial pattern include prostate, breast, ovarian, and colon cancers. Research efforts have been directed at finding genes associated with various cancers that could identify high-risk individuals for screening and early detection.

The ACS estimates that 50% of all cancers are caused by one or more of nearly 500 different cancer-causing agents (e.g., tobacco use, viruses, chemical agents, physical agents, drugs, alcohol, hormones).<sup>178</sup> Etiologic agents capable of initiating the malignant transformation of a cell (i.e., carcinogenesis) are called *carcinogens*. The study of *viruses* as carcinogens is one of the most rapidly advancing areas in cancer research today.

Researchers now have evidence that viruses play a role in the pathogenesis of cervical carcinomas, some hepatomas, Burkitt's lymphomas, nasopharyngeal carcinomas, adult T-cell leukemias, and indirectly, many Kaposi's sarcomas.<sup>40</sup> Viruses, such as the human immunodeficiency virus (HIV), the causative agent of acquired immunodeficiency syndrome (AIDS), weaken cell-mediated immunity, resulting in malignancies.

*Chemical agents* (e.g., tar, soot, asphalt, dyes, hydrocarbons, oils, nickel, or arsenics) and *physical agents* (e.g., radiation or asbestos) may cause cancer after close and prolonged contact with these agents. Most people affected by chemical agents are industrial workers. Radiation exposure is usually from natural sources, especially ultraviolet radiation from the sun, which can cause changes in deoxyribonucleic acid (DNA) structure that lead to malignant transformation. Notable exceptions include past history of radiation treatment for acne, thymus, or thyroid conditions. Basal and squamous cell carcinomas and malignant melanoma are all linked to ultraviolet exposure. See further discussion of chemical and physical agents in Chapter 4.

Some *drugs*, such as cancer chemotherapeutic agents, are in themselves carcinogenic. Cytotoxic drugs, including steroids, decrease antibody production and destroy circulating lymphocytes. Cancer clients treated with chemotherapy are at risk for future development of leukemia and other cancers.

*Hormones* have been linked to tumor development and growth, such as estrogen stimulating the growth of the endometrial lining, which over time becomes anaplastic. Other types of cancer occurring in target or hormone-responsive tissues include ovary and prostate cancers.

Excessive *alcohol* consumption is associated with cancer of the mouth, pharynx, larynx, esophagus, and pancreas. It can also indirectly contribute to liver cancer (i.e., alcohol causes liver cirrhosis, which is associated with cancer). The possible association between alcohol and breast cancer is under investigation. The pathophysiological link remains unclear, but researchers postulate that alcohol influences the metabolism of estrogen, and increased estrogen exposure is a known risk factor for breast cancer (see the section on Breast Cancer in Chapter 20).

## RISK FACTORS

Advancing age is one of the most significant risk factors for cancer. In addition to age and the carcinogens described earlier in the section on Etiologic Factors, predisposing factors also influence the host's susceptibility to various etiologic agents (Box 9-3), which are discussed further in the next section of this chapter.

### Box 9-3

#### CANCER RISK FACTORS

- Advancing age
- Previous cancer
- Lifestyle or personal behaviors
  - Tobacco use
  - Diet and nutrition (high fat, low fiber)
  - Obesity/type 2 diabetes
  - Alcohol use
  - Sexual and reproductive behavior
  - Physical inactivity
- Exposure to viruses
  - Human papillomavirus (HPV)
  - Epstein-Barr virus (EBV)
  - Hepatitis B virus (HBV)
  - Hepatitis C virus (HCV)
  - *Helicobacter pylori*
  - Herpesvirus 8
- Exposure to hormones (e.g., estrogen, testosterone)
- Geographic location and environmental variables (see Chapter 4)
- Previous cancer treatment (e.g., radiotherapy)
- Gender
- Ethnicity
- Socioeconomic status
- Occupation (see Chapter 4)
- Heredity (family history of cancer)
- Presence of precancerous lesions, polyps, or other lesions
- Stress
- Inflammatory bowel disease (IBD)

Nine modifiable risk factors are responsible for more than one-third of cancer deaths worldwide (tobacco, alcohol, obesity, inactivity, diet/nutrition, unsafe sex, urban air pollution, indoor smoke from household fuels, or contaminated injections in health care settings). Of these, smoking and alcohol consumption are the most damaging. This means that even without the potential benefits of early detection and treatment, at least one-third of cancer deaths are preventable.<sup>39,200</sup>

Experimental and epidemiologic evidence has established an association between at least eight viruses and various cancer sites. At least 10% of cancer worldwide is caused by viruses, tobacco, and diet. Some risk factors are interactive and become exponential rather than additive (e.g., alcohol and smoking for oral pharyngeal cancers).

There is no evidence to support popular theories that some people are more likely to develop cancer because of specific personality traits such as anger, hostility, frustration, sexual repression, or conflicted parent-child relationship. Additionally, cancer survival is not predicted by personality type, including neuroticism, extroversion, or low self-esteem.<sup>75,128</sup>

## Aging

Age over 50 years (some experts say age over 40 years) is a significant risk factor for the development of cancer. The association of cancer and aging is becoming more common because of the aging of the general population. The median age for all cancer is approximately 70 years

and will become even older over the next several decades.<sup>52</sup> The risk of multiple diseases (comorbidity) also increases with age, creating limitations in the life expectancy of individual aging adults and enhancing the likelihood of treatment complications.

Older people may be more susceptible to cancer simply because they have been exposed to carcinogens longer than younger people. The effects of age on immune function and host defense are being studied to determine what the association is between cancer and age (see the section on Aging and the Immune System in Chapter 7).

Factors such as accumulated nonlethal damage to DNA by free radicals, increased proinflammatory factors, and age-associated declines in DNA repair are important.<sup>52</sup> Studies on mutations in cancer-causing structures, such as telomeres (a region of DNA at the end of chromosomes), DNA repair aberrations, and dysregulation of important hormonal and immune modulators, are all being reported as potential reasons for the increasing incidence of cancer in older adults.<sup>13,183</sup>

Clues about the lifespan of a cell and about aging in general are emerging from recent research on telomeres. In normal cells, the telomere shortens each time a cell divides. Telomeres provide chromosomal stability by protecting the ends from degradation and recombination. A minimal telomere length is needed to maintain tissue homeostasis.<sup>126</sup>

The cell dies when the telomere becomes so short that it can no longer divide. An important enzyme, telomerase, helps keep normally dividing cells healthy by rebuilding the telomeres. Telomerase normally shuts down when cells are mature, but in cancer, the enzyme enables cancer cells to grow with unlimited cell divisions. Telomerase is active in up to 85% of all human cancers.<sup>25,26,145</sup> See also the section on Cellular Aging in Chapter 6. This understanding has led to discoveries regarding the lifespan of human cells, their relationship to aging, and the development of many illnesses associated with aging such as cancer. It has been reported that normal cells do not divide indefinitely during the lifespan of a human because of a phenomenon called the *Hayflick limit* and a stopping process or permanent growth arrest called *cellular senescence*.

The Hayflick limit was discovered by Leonard Hayflick in 1965.<sup>79</sup> Hayflick observed that cells dividing in cell culture divided about 50 times before dying. As cells approach this limit, they show more signs of old age. For most differentiated cells the limit to the number of times a cell divides has been determined in all cell types. The human limit is around 52, but there is some variation from cell type to cell type and more significantly, from organism type to organism type (e.g., mice and humans). This limit has been linked to the shortening of telomeres and is believed to be one of the causes of aging. Telomeres may act as cellular clocks that control aging. This is called the *telomere theory of aging*. If the shortening of telomeres can be slowed or prevented, life expectancy may be extended but perhaps at a higher risk of tumorigenesis.<sup>83</sup>

Many *in vitro* and *in vivo* studies support the idea that telomere length is strongly correlated with lifespan.

Longer telomeres have been associated with shorter lifespan (e.g., mice have very long telomeres and a short lifespan; the opposite is true for humans). Telomeres shorten progressively with each cell division; when a critical telomere length (Hayflick limit) is reached, the cells undergo senescence and subsequently apoptosis (programmed cell death).<sup>83</sup>

An alternate view is the *theory of dysfunctional senescence*. Some researchers have proposed that failure of cells or tissues to enter into cellular senescence occurs as a result of defects in genomic maintenance mechanisms after years of mutation and leads to cancer.<sup>23,204</sup> In other words, cellular senescence may reduce cancer mortality rather than promote it late in life, thus positively contributing to longevity in organisms with renewable tissues.<sup>112</sup>

Cancer cells constitute one exception to the limits on cell division. It is believed that the Hayflick limit exists principally to help prevent cancer. If a cell becomes cancerous and the Hayflick limit is approaching, the cell will only be able to divide a limited number of times before it dies. Once it reaches this limiting number of divisions, the formed tumor will no longer be able to reproduce and the cells will die off.

Cancer cells that have found ways around the Hayflick limit are referred to as "immortal." Such immortal cells may still die, but the group of immortalized cells produced from cell division of an immortal cell has no limit as to how many times cell division might take place. Telomeres in immortal cells are maintained by telomerase. Irrespective of telomere length, if telomerase is active, telomeres can be maintained at a sufficient length to ensure cell survival.<sup>83</sup> This presents a unique challenge in preventing and killing cancer cells. Creating telomerase inhibitors may possibly produce a means of supporting anticancer activity.

People age 65 years and older have a risk of cancer development much greater than younger persons, and some cancers in the older adult population seem to be biologically different from those in younger people. For example, the poor prognosis for older adults with acute leukemia is not just due to poor tolerance of aggressive chemotherapy but is more likely associated with cytogenetic resistance to chemotherapy.<sup>90</sup>

All the highest-incidence cancers affect older adults in larger numbers. In both men and women over 65 years, cancers of the colon/rectum, stomach, pancreas, and bladder accounted for two-thirds to three-fourths of the total number of these malignancies. More than 65% of lung cancers and 50% of non-Hodgkin's lymphomas occur in older men and women; 77% of the cases of prostate cancer occurred in men older than 65 years; and 48% of breast cancer and 46% of ovarian cancer occurred in women over 65 years.<sup>218</sup>

As previously mentioned, malignancies of the lung, colon/rectum, breast, and prostate account for the highest number of cancer deaths in the United States. Malignancies of the pancreas, stomach, ovary, and bladder and non-Hodgkin's lymphomas are also a major cause of cancer deaths. For each of these cancers, more than one-half of the cancer deaths occur in persons older than 65 years.<sup>218</sup>

## Lifestyle

Lifestyle or personal behaviors, such as tobacco use, diet and nutrition, alcohol use, and sexual and reproductive behavior, are cited as risk factors for the development of cancer. Lifestyle-related risk factors for cancer combined with cancer-causing substances in the environment and the presence of genes that increase the risk of cancer account for 70% of the total risk for developing cancer.

### Tobacco

Both epidemiologic and experimental data support the conclusion that tobacco (including smokeless tobacco) is carcinogenic and remains the most important cause of cancer. Tobacco use accounts for approximately 30% of cancer deaths, with lung cancer now the leading cancer causing deaths in both genders.<sup>42</sup> Cigarette smoking is related to nearly 90% of all lung cancers, and accumulating evidence suggests that cigarette smoking increases the incidence of cancer of the bladder, pancreas, and to a lesser extent, the kidney, larynx, oral cavity, and esophagus.

### Diet and Nutrition

The major role of diet and nutrition in affecting cancer risk is well established.<sup>33,619</sup> Consumption of a poor diet may blunt the immune system's natural defense mechanisms against genetic damage caused by long-term exposure to an environmental carcinogen. Diet and nutrition can directly influence various hormonal factors affecting growth and differentiation in the carcinogenic process. A healthful diet is thought to act, at least in part, to detoxify carcinogens and to inhibit certain processes in carcinogenesis, particularly at the stage of growth and spread. Diet and nutrition can influence these processes (positively or negatively) by providing bioactive compounds to specific tissues via the circulatory system or by modulating hormone levels.

Differences in certain dietary patterns among populations explain a proportion of cancers. These dietary patterns in combination with physical inactivity contribute to obesity and metabolic consequences such as increased levels of growth factor, insulin, estrogen, and possibly testosterone. These hormones tend to promote cellular growth.<sup>68</sup>

A history of obesity and/or type 2 diabetes are risk factors for breast, prostate, and colorectal cancer. Excess weight also contributes to cancers of the uterus, kidney, esophagus, pancreas, and gallbladder.<sup>21,144</sup> Fat (adipose tissue) as an endocrine gland and its role in cancer is discussed in Chapter 11.

It is estimated that approximately one-third of cancer mortality in developing countries may result from dietary causes.<sup>7,210</sup> The intake of cured, pickled, smoked, salted, and preserved food has been conclusively linked to stomach cancer, and it is suspected that there is a correlation between the amount of fat in the diet and the incidence of colorectal cancer in the United States.<sup>21</sup> There is a similar correlation between excessive red meat consumption (defined as beef, pork, or lamb) and prostate, colon, and/or rectal cancer.<sup>103</sup> Epidemiologic data also

suggest links between fat intake and prostate and ovarian cancers, although not all findings are consistent.<sup>80</sup>

Reduction of cancer risks for most epithelial tumors, especially colorectal cancer, has been demonstrated repeatedly in the presence of increased dietary intake of fresh fruits and vegetables and fiber. High cruciferous vegetable consumption may reduce bladder cancer risk and the risk of non-Hodgkin's lymphoma.<sup>120,220</sup> Although the role of fruits and vegetables and their antioxidant qualities in reducing free radicals that contribute to cancer of various sites has been proved, a recent report suggests the recommendation to eat an abundance of fruits and vegetables to reduce cancer risk may be overstated. Cardiovascular benefits were much more evident; the 30% to 50% reduction in cancer that research suggested previously was not supported.<sup>209</sup> Experts reviewing the results of this study questioned the methodology used and pointed out that choosing healthy foods, such as fruits and vegetables, to meet caloric and nutritional needs is more protective than a diet laden with sugar, fat, or low-nutrient foods.

Additionally, cancer survivors are often highly motivated to improve nutrition and begin an exercise program after receiving a diagnosis of cancer. The ACS continues to publish and update best clinical practices related to optimal nutrition and physical activity during and after cancer treatment. In the absence of scientific evidence that diet, nutrition, and physical activity can prevent cancer recurrence, reasonable conclusions are offered.<sup>47,103</sup>

Cancer and cancer treatment can cause profound metabolic and physiologic alterations affecting the body's needs for adequate nutritional intake. Gastrointestinal side effects of treatment can lead to loss of appetite and weight loss accompanied by malnutrition. All the major treatment modalities (e.g., surgery, chemotherapy, or radiation) can adversely impact how the body digests, absorbs, and uses food. Preserving lean body mass is an important goal of nutritional care for survivors, especially during active cancer treatment.<sup>174</sup>

The use of nutritional supplements and antioxidants remains controversial. Until more evidence is available that suggests more benefit than harm, the Institute of Medicine suggests it is prudent for cancer survivors receiving chemotherapy or radiation therapy to avoid exceeding more than 100% of the daily value for antioxidant-type vitamins during the treatment phase.<sup>92</sup>

### Alcohol

Alcohol consumption has been linked to increased rates of cancer of the mouth, pharynx, larynx, esophagus, liver, breast, and probably colon. In people who have been diagnosed with cancer, alcohol intake could also affect the risk for new primary cancers of these sites. Alcohol intake can increase the circulating levels of estrogens, theoretically increasing the risk for breast cancer recurrence.<sup>166,187</sup>

With tobacco use, alcohol interacts with smoke synergistically, increasing the risk of malignant tumors by acting as a solvent for the carcinogenic smoke products and thus increasing the absorption of carcinogens. Evidence is suggestive (but not yet convincing) in associating

alcohol consumption and cancers of the colon, pancreas, breast, bladder, and head and neck.<sup>80</sup>

### Sexual and Reproductive Behaviors

Sexual and reproductive behaviors are linked to the risk of developing various cancers. For example, the risk of developing cervical cancer is linked with early sexual intercourse and multiple partners. Pregnancy and childbearing seem to be protective against cancers of the endometrium, ovary, and breast. Prolonged lactation may also have a significant impact in the reduction of breast cancer risk by reducing the cumulative exposure of breast tissue to estrogen.<sup>80</sup> Other risk factors for breast cancer are discussed in Chapter 20.

### Hormonal Exposure

Hormonal exposure is a factor for women. For example, prolonged exposure to estrogen (e.g., early onset of menses, menopause after age 50, nulliparity or no children, first child after age 30, never breastfed children, or use of first-generation oral contraceptives before 1975) is a risk factor for estrogen-sensitive breast cancer.

Prolonged use of estrogen hormone replacement therapy for relief of menopausal symptoms has been linked with increased rates of breast cancer. Data from the Women's Health Initiative (WHI) resulted in a halt to the routine use of estrogen and progestin in combination (Prempro) in 2002 and estrogen alone (Premarin) in 2004. When compared with a placebo group, it was clear that hormone users were experiencing more breast cancer, heart disease, stroke, and blood clots. Estrogen showed some benefit, but it was not enough to outweigh the risks.<sup>215</sup>

Growth factors, such as insulin growth factor 1 (IGF-1), and hormones, such as estrogen and testosterone, are considered risk factors linked with cancers other than breast and prostate (e.g., lung, endometrial, and colon). A growing body of recent literature indicates that besides its essential role in growth and development, growth hormone may play a role in the development and progression of cancer.<sup>147</sup>

The *insulin-cancer hypothesis* postulates that complex links between excess body weight, the insulin-IGF axis, and cancer suggest molecular mechanisms are present that lead to increased availability of IGF-1, providing a cellular environment that favors tumor formation.<sup>162</sup> Growth factor signaling pathways appear to be up-regulated in hormone-resistant tumors and interact with estrogen receptor signaling, which remains functional even after long-term endocrine deprivation. Intensive research efforts to develop antitumor agents that inhibit IGF signaling in human tumors are underway.<sup>74</sup>

### Geographic Location and Environmental Variables

The incidence of different types of cancer varies geographically. People living in rural areas are less likely to use preventive screening services or to exercise regularly. Colon cancer is more prevalent in urban than in rural areas, but in rural areas, especially among farmers, skin cancer is more common. Availability of specialty care is a possible contributing issue for this group of people.

The greater susceptibility of certain geographic areas within the United States is probably related to exposure to different carcinogens.<sup>35</sup> The increased incidence of cancer found in urban areas may be related to the increased pool of minorities, increased poverty represented in this group, local smoking ordinances, and diet (e.g., cost and availability of fresh fruits and vegetables).<sup>150</sup>

Occupational or environmental exposure to chemicals (e.g., herbicides, insecticides, dyes), fibers (e.g., asbestos), radon, and air pollution is a risk factor for lung and hematologic cancers. Researchers are investigating the possible causal relationship between environmental exposure and the increased incidence of childhood cancers. The U.S. Environmental Protection Agency (EPA) has identified the carcinogenic effects from hazardous exposures. Heritable genetic and chromosomal mutations caused by environmental or occupational exposures to agents (e.g., chemicals, radiation) can be passed on to the next generation. For further discussion, see Chapter 4.

According to the seventh report on the Biological Effects of Ionizing Radiation (BEIR VII) issued by the National Academy of Science, exposure to even low-dose imaging radiology (including computed tomography [CT] scans) can result in the development of malignancy. Exposure to medical x-rays is linked with leukemia, thyroid cancer, and breast cancer. There is a 1 in 1000 chance of developing cancer from a single CT scan of the chest, abdomen, or pelvis. The latency period for leukemias is 2 to 5 years and 10 to 30 years for solid tumors.<sup>129</sup>

### Ethnicity

Despite advances in cancer diagnosis, treatment, and survival, racial and ethnic minorities suffer disproportionately from cancer. Poverty has emerged as a significant factor influencing poor cancer outcomes for all races, especially among minorities.<sup>156</sup> Inequities in insurance status adversely affect low income families, preventing individual members from obtaining screening, access to quality care, or the entire range of cancer care available.<sup>185</sup>

In particular, racial disparities exist between Caucasians and other groups, especially African Americans. Overall, incidence and mortality from cancer is 10% higher in African Americans compared to Caucasians.<sup>18,185</sup> Studies have shown that equal treatment yields equal outcomes among individuals with equal disease.<sup>12,93</sup> At present, this increased incidence is attributed to preventable risk factors such as the absence of early screening, delayed diagnosis, and smoking and diet. The number of African American men who smoke is decreasing, but the incidence of lung cancer and other smoking-related diseases remains high, possibly because black men tend to smoke cigarettes with a higher tar and nicotine content. The incidence rates of prostate cancer among black men are at least 50% higher than rates for men of other ethnic groups.<sup>96</sup>

Lung cancer is the leading cause of cancer death among African American women. The number of African American women (aged 45 to 54 years) who have died from lung cancer has increased 30% over the last 2 decades.<sup>212</sup>

The number of African American women of all ages who have died from breast cancer has risen nearly 20% over the last 25 years. Breast cancer is the second leading cause of death for African American women. Colorectal cancer has increased in both African American men and women; black women are twice as likely to develop cervical cancer and nearly three times as likely to die from it as other women; African American men have the world's highest rate of prostate cancer.<sup>99</sup>

Some specific forms of cancer affect other ethnic groups at rates higher than the national average (e.g., stomach and liver cancers among Asian-American populations and colorectal cancer among Alaska Natives). African Americans have a lower incidence of bladder cancer but higher mortality rates compared to Caucasians.<sup>201</sup> The incidence of and mortality rates for esophageal cancer are twice as high for African Americans compared to Caucasians.<sup>14</sup>

Differences among ethnic groups represent a challenge to understand the reasons and an opportunity to reduce illness and death while improving survival rates. Hispanic people originate from 23 different countries with a wide range of diversity. Racial variations exist in tumor growth, susceptibility, and treatment response. For example, Latino populations have different drug resistance gene expression than non-Latino whites.<sup>138</sup>

Hispanics are the poorest minority group with the highest uninsured rate of all groups.<sup>138</sup> They have higher rates of cervical, esophageal, gallbladder, and stomach cancers. New cases of female breast and lung cancers are increasing among Hispanics, who are diagnosed at later stages and have lower survival rates than whites.

Asian Americans have a unique situation in that they are the only racial/ethnic group to experience cancer as the leading cause of death with proportionately more cancer of infectious origin (e.g., human papillomavirus-induced cervical cancer, hepatitis B virus-induced liver cancer, and stomach cancer) than any other minority group. Cultural barriers to intervention exist such as overcoming resistance to physician visits, reducing tobacco use, and increasing exercise.<sup>28</sup>

### Precancerous Lesions

Precancerous lesions and some benign tumors may undergo later transformation into cancerous lesions and tumors. Common precancerous lesions include pigmented moles, burn scars, senile keratosis, leukoplakia, and benign adenomas or polyps of the colon or stomach. All such lesions need to be examined periodically for signs of changes.

### Stress

Recent research suggests a strong link between stress and cancer. Chronic physical or emotional stress can cause hormonal or immunologic changes or both, which in turn can facilitate the growth and proliferation of cancer cells. There is substantial evidence from both healthy populations and people with cancer that links psychologic stress with immune down-regulation. Distress and depression are associated with two important processes for carcinogenesis: poorer repair of damaged DNA and alterations in apoptosis.

Both aging processes and psychologic stress affect the immune system; in fact, the effects of stress and age are interactive. Psychologic stress can both mimic and exacerbate the effects of aging. Older adults often show greater immunologic impairment to stress compared to younger adults.<sup>72</sup> Conversely, the possibility that psychologic interventions and social support may enhance immune function and survival is under further investigation.<sup>100</sup> Psychologic modulation of immune function is now a well-established phenomenon. Psychoneuroimmunology and psychoneuroendocrinology research focuses on how the brain and body communicate with each other in a multidirectional flow of information that consists of hormones, neurotransmitter/neuropeptides, and cytokines.<sup>205</sup>

Proponents of psycho-oncology (psychoneuroimmunology and cancer) suggest that advances in mind-body medicine research combined with healthy nutrition and lifestyle choices can have a significant impact on health, health maintenance, disease, and disease prevention, including cancer.<sup>99,205</sup> See the section on Psychoneuroimmunology Theory in Chapter 1; see also the section on Stress in Chapter 3.

## PATHOGENESIS

Early in the study of cancer the concept that neoplasia originates in a single cell by acquired genetic change was proposed and remains today the view of cancer pathogenesis most supported by experimental evidence. This hypothesis, called the *somatic mutation theory*, was first substantiated when investigations of tumors confirmed that tumor cells are characterized by chromosomal abnormalities, numerical and structural.

The discovery that chromosomal aberration is one of the basic mechanisms of tumor cell proliferation laid the foundation of modern cancer cytogenetics (study of chromosomes in cancer). Chromosomal changes can include addition or deletion of entire chromosomes (numerical changes) or translocations, deletions, inversions, and insertions of parts of chromosomes (structural changes). Translocations occur when two or more chromosomes exchange material and are common in leukemias and sarcomas. Deletions or losses of chromosomal material are common in epithelial adenocarcinomas of the large bowel, lung, breast, and prostate. Chromosomal deletions may lead to neoplastic development when a tumor suppressor gene is lost. Chromosomal inversions and insertions are less common but still cause abnormal juxtaposition (side-by-side placement) of genetic material.<sup>164</sup>

At first the question arose: are acquired chromosomal abnormalities the cause of the neoplastic changes in cells or merely the result of the neoplastic state? Chromosomal banding techniques developed in the 1970s have allowed precise identification of chromosomal changes. This information, along with molecular genetic techniques developed during the 1980s, has enabled researchers to investigate this question by examining tumor cells at the level of individual genes.

From these studies, two functionally different classes of cancer-relevant genes have been detected: (1) the dominant oncogenes and (2) the recessive tumor suppressor genes. Both gene classes have been detected at just those chromosomal sites that are visibly involved in cancer-associated rearrangements. To date, over 100 genes have been found to be structurally or functionally altered after neoplasia-associated chromosomal abnormalities.

Exactly how these chromosomal changes contribute to the malignant process remains unclear. Chromosomal rearrangements may lead to oncogene activation, either by a regulatory change causing increased production of normal oncogene-encoded peptides or by creating a deranged oncogene template that codes for an abnormal protein product.

Another proposed mechanism suggests that chromosomal changes inactivate a tumor suppressor gene through chromosomal deletion. Loss of tumor suppressor genes is suspected because chromosomal regions found to be consistently missing in tumor cells have been observed in carcinomas of the lung, breast, bladder, and kidney.

An important tumor suppressor gene currently under study is p53. The p53 gene appears to trigger programmed cell death (apoptosis) as a way of regulating uncontrolled cellular proliferation. Mutations in the p53 tumor suppressor gene result in loss of the ability of the gene protein to bind with DNA and act as a suppressor for the division of that cell.<sup>139</sup> Mutations in p53 are associated with resistance to chemotherapy and radiation therapy.

Additionally, researchers have demonstrated that cancer cells develop multiple mechanisms of their own to evade apoptosis. Cancer cells can inactivate proapoptotic factors or up-regulate antiapoptotic factors. Strategies to induce apoptosis specifically in tumor cells are currently under investigation. One proapoptotic protein that has been shown to induce apoptosis in a wide variety of tumor cells is a member of the tumor necrosis factor (TNF) superfamily called *TNF-related apoptosis-inducing ligand* (TRAIL).<sup>27,167</sup>

Another genetic suppressor of cell growth and division also plays a part in the aging process. As cells divide and grow older, there is continuous progressive shortening of the end portions of the chromosomes or telomeres of those cells. Studies of human fibroblasts and other human tissues have shown a very close association between the development of cancer and the overproduction of the enzyme telomerase. When this enzyme is present, it prevents the telomeres from shortening, thus lengthening the lifespan of the cell indefinitely. Telomerase has been found to be present in more than 85% of human cancer cells but is absent in most normal human tissues.<sup>145,168,202</sup>

Recurrent or persistent inflammation may induce, promote, or influence susceptibility to carcinogenesis by causing DNA damage, inciting tissue reparative proliferation, and/or creating an environment (soil) rich with cytokines and growth factors. Chronic inflammation and the metabolic products of phagocytosis are often accompanied by the excessive formation of reactive oxygen and nitrogen that are potentially damaging to DNA, lipoproteins, and cell membranes.<sup>176</sup>

Although much remains to be learned about the cascade of genetic changes for every kind of cancer, increasing understanding may suggest a means for interrupting the genetic events leading to cancer and for diagnosing the early stages of tumorigenesis. Current research continues to focus on the following major areas of biologic study<sup>53</sup>:

- Regulation of cellular proliferation and expression of oncogenes and tumor suppressor genes
- Telomere length and telomerase
- Free radical-induced DNA damage (see Fig. 5-2) and regulation of apoptosis
- Immune function and response (e.g., senescence, surveillance, enhancement)
- Cellular and humoral factors associated with the chronic inflammatory process

## Current Theory of Oncogenesis

The study of viruses in tumors has led researchers to discover small segments of genetic DNA called *oncogenes*. Oncogenes, also called *cancer-causing genes* or *protooncogenes*, have the ability to transform normal cells into malignant cells, independently or incorporated with a virus. Oncogenes are thought to be the abnormal counterparts of protooncogenes, which aid in regulating biologic functions, such as cell division, in normal cells.

Oncogenes may be activated by carcinogens, at which point they alter the regulation of growth in the cell. Oncogenes force a cell to grow even when its surroundings contain none of the cues that normally provoke growth. Oncogenes are hyperactivated versions of normal cellular growth-promoting genes. By releasing strong, unrelenting growth-stimulating signals into a cell, oncogenes can drive cell growth ceaselessly.

Researchers have also discovered a group of regulatory genes, called *antioncogenes* and now called *tumor suppressor genes*, that have the opposite effect of oncogenes. When activated, tumor suppressor genes can regulate growth and inhibit carcinogenesis. Tumor suppressor genes are the "brakes" to the "stuck accelerator" of the activated oncogene (e.g., p53 or telomeres). When defects in the oncogene occur simultaneously with inactivation of growth-suppressing genes, aggressive cell proliferation takes place with the creation of certain types of tumor cells.

## Tumor Biochemistry and Pathogenesis

Carcinogenesis is the process by which a normal cell undergoes malignant transformation. Usually, it is a multistep process, involving progressive changes after genetic damage to or alteration of cellular DNA through the development of hyperplasia, metaplasia, dysplasia, carcinoma *in situ*, invasive carcinoma, and metastatic carcinoma in that order.<sup>123</sup> These discrete stages in tumor development suggest that a single altered gene only suffices to push a cell part of the way down the path to actual malignancy. The process is completed when multiple, successive changes occur in distinct cellular genes, including activation or overexpression of oncogenes and loss or mutation of tumor suppressor genes.

The number of genetic events required for conversion of normal cells to malignant cells is still debated, but, at least in the case of many solid tumors (e.g., colon carcinomas), this number may be as great as seven or eight. This high number of genetic events may imply that genetic instability occurs during cancer progression.<sup>123</sup> This requirement for multiple changes creates an important protective mechanism against cancer. If a small number of genetic changes sufficed to transform a normal cell into a malignant one, multiple tumors would develop easily. These multiple barriers, along with the normal circuitry inside cells, ensure that only the rare cell will sustain the requisite number of changes for making a cancer cell. On the other hand, cancer has developed multiple methods centering on genetic mutation to promote self-survival and perpetuation. The pliability of cancer cells to mutate in several different phenotypes in an attempt to find one that will survive and colonize at a metastatic site makes finding effective treatment difficult at best.

## INVASION AND METASTASES

Malignant tumors differ from benign tumors in their ability to metastasize or spread from the primary site to other locations in the body. Metastasis occurs when cells break away from the primary tumor, travel through the body via the blood or lymphatic system, and become trapped in the capillaries of organs. From there, they infiltrate the organ tissue and grow into new tumor deposits. Cancer can also spread to adjacent structures and penetrate body cavities by direct extension. For example, ovarian tumors frequently shed cells into the peritoneal cavity where they grow to cover the surface of abdominal organs and cause ascites.

Patterns of metastasis differ from cancer to cancer. Although there is no clear explanation of the exact mechanism of metastasis, certain cancers tend to spread to specific organs or sites in the body in a predictable manner (Table 9-2). The five most common sites of metastasis are the lymph nodes, liver, lung, bone, and brain. The spread of cancer may be influenced by a variety of host factors such as the aging or dysfunctional immune system, increasing age, hormonal environment, pregnancy, and stress. Factors that may slow the spread of metastasis include radiation, chemotherapy, anticoagulants, steroids, and other antiinflammatory agents.

## Seed Versus Soil Theory of Metastasis

Some cancers favor certain sites of metastasis over others so that metastases only occur if the cancer cell (the seed) finds a favorable microenvironment at the site of the host (the soil). Certain tumor cells seem to have specific affinity for certain organs. The idea that metastasis is organ specific was first proposed in 1889 by Stephen Paget, an English surgeon who first published the seed versus soil hypothesis to explain the pattern of metastasis.<sup>56</sup>

Studies in the 1990s showed that there is "cross-talk" between metastatic cells and the organ microenvironment. Host cells secrete growth factors that prompt tumor

cell replication and allow the tumor to take over the homeostatic mechanisms of the host. Angiogenesis, the process by which blood vessels from preexisting vessels grow into the solid tumor, is one way that tumor cells take over homeostatic mechanism for their own gain.<sup>56</sup>

Traditional cancer treatment targets the seed, whereas today's research is focused on approaches that target the soil, making the sites of metastasis unsuitable for the growth of cancer cells. There are many challenges in preventing metastasis because the microenvironments of metastasis sites can be very different. For example, lung cancer that spreads to the femur can behave very differently from lung cancer that spreads to the spine. Treatment that is optimal in the primary organ may not work in the metastatic sites.<sup>140</sup>

Animal studies show that the surgical removal of a primary tumor can result in the rapid growth of previously dormant metastatic cells. Additional challenges to preventing metastases are possible if this phenomenon occurs in humans.<sup>22</sup>

## Incidence of Metastasis

Approximately 30% of clients with newly diagnosed cancers have clinically detectable metastases. At least 30% to 40% of the remaining clients who are clinically free of metastases harbor occult (hidden) metastases. Unfortunately, most people have multiple sites of metastatic disease, not all of which present at any one time. The formation of metastatic colonies is a continuous process, commencing early in the growth of the primary tumor and increasing with time.

Even metastases have the potential to metastasize; the presence of large, identifiable metastases in a given organ can be accompanied by a greater number of micrometastases that have been disseminated more recently from the primary tumor or the metastasis. The size variation in metastases and the dispersed anatomic location of metastases can make complete surgical removal of disease impossible, limiting the effective concentration of anti-cancer drugs that can only be delivered to tumor cells in metastatic colonies.

## Mechanisms of Metastasis

For rapidly growing tumors, millions of tumor cells are shed into the vascular system each day. Only a very small percentage of circulating tumor cells initiate metastatic colonies because most cells that have invaded the bloodstream are quickly eliminated. Classic isotope studies have shown that 99% of circulating potentially tumorigenic cells are killed by blood vessel turbulence within 24 hours.<sup>56,57,69</sup> Metastases of the remaining 1% require a good deal of coordination between the cancer cells and the body (Fig. 9-2).

The greater the number of invasive tumor cells in the bloodstream, the greater the probability that some cells will survive to form metastases. Metastasis is more likely to occur via the veins as opposed to the arteries because the cancer cannot break through the arterial wall. The major challenge in treating cancer is not eradicating the primary tumor because surgery or radiation is effective in

**Table 9-2** Pathways of Cancer Metastases

<b>Primary Cancer</b>	<b>Mode of Dissemination</b>	<b>Location of Primary Metastases</b>
Breast	Lymphatics	Bone (shoulder, hips, ribs, vertebrae); CNS (brain, spinal cord)
Bone	Blood (vascular or hematogenous)	Lung, pleural cavity, liver
Cervical (cervix)	Blood Local extension and lymphatics	Lungs, liver, bone then CNS Retroperitoneal lymph nodes, bladder, rectum; paracervical, parametrial lymphatics
Colorectal	Blood Direct extension Peritoneal seeding	CNS (brain), lungs, bones, liver Bone (vertebrae, hip) Peritoneum
Ewing's sarcoma	Blood	Liver, lung
Kidney	Lymph	Lung, bone, bone marrow
Leukemia	Blood	Pelvis, groin Lungs, pleural cavity, bone, liver Does not really metastasize; causes symptoms throughout body
Liver	Blood	CNS (brain)
Lung (bronchogenic sarcoma)	Blood Blood Direct extension, lymphatics	CNS (brain, spinal cord) Bone (posterior ribs first then disseminated) Mediastinum (tissue and organs between the sternum and vertebrae such as the heart, blood vessels, trachea, esophagus, thymus, lymph nodes)
Lung (apical or Pancoast's tumors)	Direct extension	8th cervical and 1st and 2nd thoracic nerves within the brachial plexus
Lymphoma	Blood Blood	CNS (brain, spinal cord), bone CNS (spinal cord)
Malignant melanoma	Lymphatics No typical pattern	Can occur anywhere including skin, visceral organs Metastases can occur anywhere; skin and subcutaneous tissue; lungs; CNS (brain); liver; GI tract; bone Bones underlying involved skin; brain
Nonmelanoma skin cancer	Usually remain local without metastases; local invasion	
Osteogenic sarcoma (osteosarcoma)	Lymphatics	Lymph nodes, lungs, bone, kidneys
Ovarian	Blood Direct extension into abdominal cavity; peritoneal fluid through the abdomen Lymphatics	CNS (brain) Nearby organs (bladder, colon, rectum, uterus, fallopian tubes)
Pancreatic	Blood	Liver, lungs; regional and distant (spread beyond the abdomen is rare)
Prostate	Lymphatics	Liver Pelvic and vertebral bones Bladder, rectum Distant organs (lung, liver, brain)
Spinal cord	Local invasion; dissemination through the intervertebral foramina	CNS (brain; spinal cord)
Stomach, gastric	Blood Local invasion	CNS (brain; spinal cord) Liver, vertebrae, abdominal cavity (intraperitoneum)
Thyroid	Direct extension Lymphatics Blood	Bone; nearby tissues of neck Regional lymph nodes (neck, upper chest, mediastinum) Distant (lung, bone)

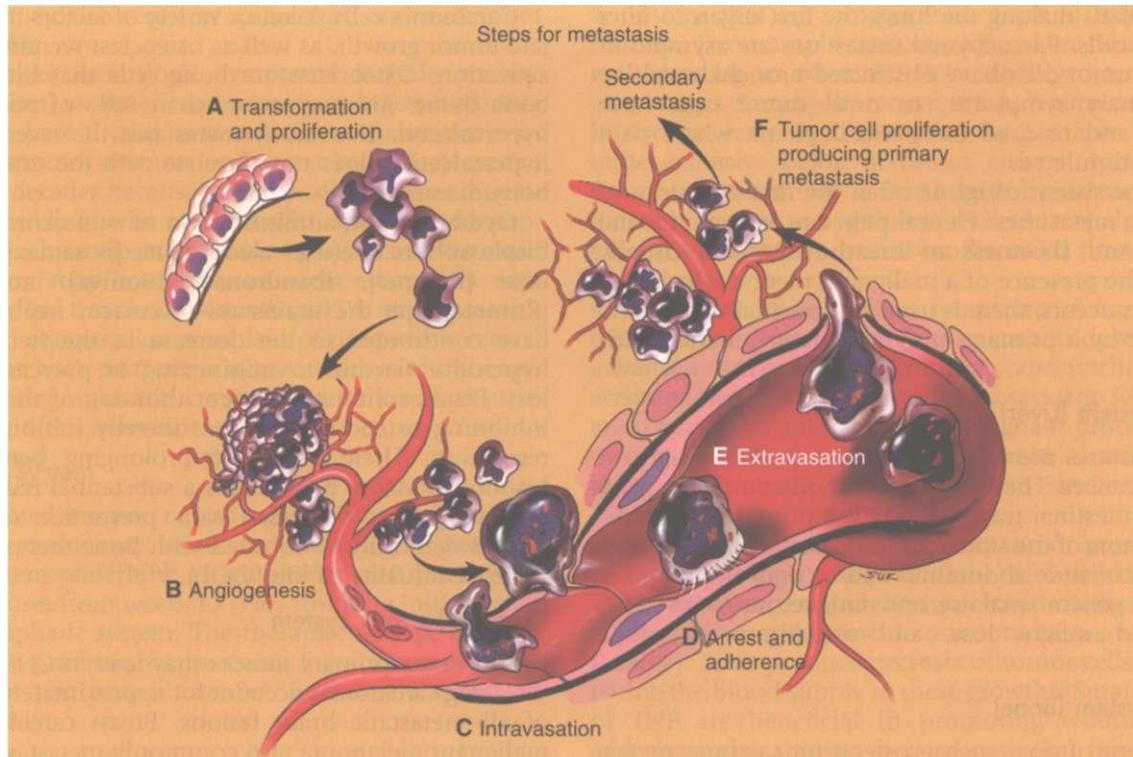
Adapted from Goodman CC, Snyder TE: *Differential diagnosis for physical therapists: screening for referral*, ed 4, Philadelphia, 2007, WB Saunders. CNS, Central nervous system; GI, gastrointestinal.

these early cases. Eradicating metastases, often already present at the time of diagnosis is the key factor to cancer cure.

A complicated series of tumor-host interactions resulting in a metastatic colony is called the *metastatic cascade* and is similar for all tumor cells. Once a primary tumor is initiated and starts to move by local invasion, then blood vessels from preexisting vessels grow into the solid tumor, a process called *tumor angiogenesis* (see Fig. 9-2).

As a normal physiologic process, angiogenesis is crucial to tissue growth, repair, and maintenance.

The ability of a tumor to grow beyond a very small mass (1 to 2 mm) depends on its ability to gain access to an adequate supply of blood and in some cases (e.g., breast and prostate) the presence of hormonal factors. The supply of blood allows the tumor to obtain essential nutrients, such as oxygen, and to eliminate metabolic waste products, such as carbon dioxide and acids. The



**Figure 9-2**

Major mechanisms of metastases. To metastasize, tumor cells must gain several unique biologic properties such as invasive growth (**A**), induction of vascular growth (**B**), vascular invasion (**C**), adherence to endothelial cells or thrombosis of peripheral sinusoids (**D**), continuation of invasive growth with extravasation (**E**), and formation of primary and secondary metastatic foci (**F**). Not all tumor cells develop all the abilities shown here; some cell clones may subspecialize and just create angiogenesis; others may invade and move on. (From Dorfman HD, Czerniak B: Bone tumors, St. Louis, 1998, Mosby.)

blood supply to tumors is provided by growth of new capillaries and larger vessels into the tumor mass from the blood supply of adjacent normal tissues.

The normal process of angiogenesis begins with the formation of endothelial cell sprouts followed by proliferation and migration of neighboring endothelial cells along the preformed extensions. The initiating event and mechanism of sprouting are unknown; in apoptotic cells, endothelial cell sprouting occurs via electrostatic signaling. Negatively charged membrane surfaces in apoptotic cells initiate the formation of directional endothelial cell sprouts that extend toward the dying cells.<sup>207</sup>

Tumor-derived proteins called *angiogenesis factors* also facilitate the use of nearby blood vessels from normal tissues and promote the growth of new blood vessels into the malignant tissue.<sup>164</sup> The actual factors involved in tumor angiogenesis are very complex, but two cytokines have been identified as primary stimulators of vascular proliferation.

Both vascular endothelial growth factor (VEGF) and fibroblast growth factor stimulate proliferation of vascular cells and even allow the newly formed blood vessels to be easily invaded by the cancer cells that are closely adjacent to them.<sup>51</sup> Increased tumor contact with the circulatory system provides tumors with a mechanism to enter the general circulation and colonize at distant sites. Antiangiogenic therapy shows promise as a strategy for cancer treatment (see the section on Treatment in this chapter).

Tumors generally lack a well-formed lymphatic network, so communication of tumor cells with lymphatic channels occurs only at the tumor periphery and not within the tumor mass. Lymphatic dissemination and hematogenous dissemination occur in parallel. Tumors excrete acidlike enzymes that dissolve the basement membrane and break through to the lymphatics. Cancer cells can enter the bloodstream where lymph nodes drain into veins (e.g., lymphatic intersection with the subclavian vein).

## Clinical Manifestations of Metastasis

Metastatic spread usually occurs within 3 to 5 years after initial diagnosis and treatment of malignancy, although some low-grade lesions can reappear as much as 15 to 20 years later. It is therefore very important to conduct a thorough past medical history as part of any client interview. Metastases occur most commonly to areas of the body that provide an environment rich in nutrition to the colonized tumor cells, such as the lung, brain, liver, and bone; metastases can be found in other areas as well (e.g., the lymph nodes, skin, ovaries, and adrenal glands).

### Pulmonary System (Lungs)

Pulmonary metastases are the most common of all metastatic tumors because venous drainage of most areas of the body is through the superior and inferior vena cavae

into the heart, making the lungs the first organ to filter malignant cells. Parenchymal metastases are asymptomatic until tumor cells have obstructed bronchi, resulting in pulmonary symptoms, or until tumor cells have expanded and reached the parietal pleura where pain fibers are stimulated.

A dry, persistent cough is often the first symptom of pulmonary metastases. Pleural pain can indicate pleural invasion, and shortness of breath (dyspnea) usually occurs in the presence of a malignant pleural effusion. If hemoptysis occurs, there is usually bronchial tissue invasion either by a primary lung malignancy or metastatic disease.<sup>199</sup>

### Hepatic System (Liver)

Liver metastases are among the most ominous signs of advanced cancer. The liver filters blood coming in from the gastrointestinal tract, making it a primary metastatic site for tumors of the stomach, colorectum, and pancreas. Symptoms include abdominal and/or right upper quadrant pain, general malaise and fatigue, anorexia, early satiety and weight loss, and sometimes low-grade fevers.

### Skeletal System (Bone)

Primary bone tumors, such as osteogenic sarcoma, metastasize initially to the lungs, whereas a large proportion of cancer cases metastasize first to the bone, often with a poor prognosis (see also Chapter 26). Bone is one of the three most favored sites of solid tumor metastasis, indicating that the bone microenvironment provides fertile ground for the growth of many tumors. Although lung, breast, and prostate are the three primary sites responsible for most metastatic bone disease, tumors of the thyroid and kidney, lymphoma, and melanoma can also metastasize to the skeletal system.

Bone metastases may be the osteolytic type, marked by areas of decreased bone density, or osteoblastic, appearing as areas of dense scarring and increased bone density. Osteolytic metastases predominate in lung, kidney, and thyroid cancer; breast is primarily osteolytic but can be osteoblastic and prostate is usually but not always osteoblastic. The axial skeleton is most commonly involved with spread to the spine, pelvis, ribs, proximal femora, proximal humeri, and skull.<sup>125</sup>

The primary symptom associated with bone metastases is pain. Pain is usually deep and worsened by activity, especially weight bearing. Disabling pathologic fractures, especially of the vertebral bodies and proximal ends of the long bones, may occur in up to one-half of people with osteolytic metastases and are sometimes one of the first signs of a malignant process.<sup>73</sup> Blastic lesions often result in an elevated serum alkaline phosphatase, whereas lytic lesions may not.<sup>118</sup>

Hypercalcemia (abnormally high concentration of blood calcium) is a frequent complication of neoplastic disease and is associated with bony metastases, particularly osteolytic lesions as a result of increased bone resorption. The presence of tumor cells in the bone disturbs the balance between new bone formation and bone resorption, resulting in abnormal bone remodeling.

Carcinoma cells secrete a variety of factors that stimulate tumor growth, as well as osteoclast recruitment and activation. Osteoclasts are bone cells that break down bone tissue. Although more than 80% of people with hypercalcemia have bony metastasis, the severity of the hypercalcemia does not correlate with the extent of the bony disease.

Hydration and administration of oral or intravenous bisphosphonates (e.g., alendronate [Fosamax], risedronate [Actonel], ibandronate [Boniva], zoledronate [Zometa]) are the mainstays of current treatment and have contributed to the decrease in the frequency of hypercalcemia and to minimizing or preventing bone loss. Bisphosphonates prevent thinning of the bone by inhibiting osteoclast function, thereby inhibiting bone resorption. There is no life-prolonging benefit with bisphosphonates, but there is a substantial reduction of morbidity (e.g., decreased pain, prevention of fracture and/or deformity) associated with bone metastases and improved quality of life (QOL).<sup>17,32,40,85</sup>

### Central Nervous System

**Brain.** Many primary tumors may lead to CNS metastases. Lung carcinomas account for approximately one-half of all metastatic brain lesions. Breast carcinoma and malignant melanoma also commonly metastasize to the brain. Metastatic disease in the brain is life-threatening and emotionally debilitating. Metastatic brain tumors can increase intracranial pressure, obstruct the normal flow of cerebrospinal fluid, change mentation and contribute to cognitive impairment, and reduce sensory and motor function. The management of cognitive impairments is important, and the therapist can use the same strategies known for people with traumatic brain injury (see Chapter 33).

Clinical manifestations of brain metastases depend on the location, either in the brain or outside the brain in the bony cranium exerting compression externally. The therapist can look at CT scan results, see the location of pathologic conditions, and correlate these to signs and symptoms observed clinically (see Table 30-3). Primary tumors of the CNS rarely develop metastases outside the CNS despite the highly invasive capacity of these tumors. Microscopically, some CNS (brain) tumor cells (astrocytomas) may spread widely within the CNS but rarely metastasize outside it.

Tumor cells traveling from the lung via the pulmonary veins and carotid artery can result in metastases to the CNS. Lung cancer is the most common primary tumor to metastasize to the brain. Any neurologic sign may be the presentation of a silent lung tumor.<sup>73</sup>

**Spinal Cord.** Metastatic involvement of the vertebrae may result in epidural spinal (usually anterior) cord compression. In addition, severe, destructive osteolytic lesions can lead to fracture and fragility of one or more vertebral bodies. In such cases, compression of the cord occurs as a result of the subsequent deformity.<sup>124</sup> Spinal cord and nerve root compression cause either insidious or rapid loss of neurologic function. This compression phenomenon occurs in approximately 5% of people with systemic cancer and is most often caused by carcinoma of the lung, breast, prostate, or kidney. Lymphoma and multiple

myeloma may also result in spinal cord and nerve root compression.

The earliest neurologic symptoms include gradual onset of distal weakness and sensory changes, including numbness, paresthesias, and coldness. The incidence of permanent motor dysfunction has markedly decreased in the past 2 decades because of earlier diagnosis and treatment.<sup>40</sup> The client who presents with spinal cord symptoms caused by metastatic epidural disease and resultant compression may have only transient symptoms with proper medical treatment. More than 95% of people with spinal cord compression complain of progressive central or radicular back pain often aggravated by recumbency, weight bearing, sneezing, coughing, or Valsalva's maneuver. Sitting often relieves it.

### Lymphatic System

Cancer-related surgery or radiation treatment affecting the lymph nodes may result in dysfunction of the lymphatic system presenting as lymphedema. It has a wide range of onset from weeks to years from the initial insult to the lymphatic system. The therapist may be the first health care professional to assess for abnormalities or changes in the extremities. See further discussion in Chapter 13.

### Diagnosis of Metastasis

Metastases usually reproduce the cellular structure of the primary growth well enough to enable a pathologist to determine the site of the primary tumor. For example, bone metastases from a carcinoma of the thyroid not only exhibit a microscopic structure similar to the original tumor but also may produce thyroid hormone. Sometimes, symptoms of a cancer will present in the metastatic site rather than the site of origin (primary site). If the primary tumor cannot be found, the malignant tissue is called *carcinoma of unknown primary*. Special histologic stains can be done on the unknown tissue and compared to slides of a previous malignancy to determine similarity.

### Cancer Recurrence

Disease-free survival describes the time between diagnosis and recurrence or relapse. Recurrences may be local, regional, disseminated, or a combination of these. The most important predictors of recurrent cancer are the stage at the time of initial therapy and histologic findings. Recurrence of cancer may be first recognized by the return of systemic symptoms associated with paraneoplastic phenomena. The metabolic or toxic effects of the syndrome (e.g., hypercalcemia or hyponatremia) may constitute a more urgent hazard to life than the underlying cancer.

## CLINICAL MANIFESTATIONS

### Local and Systemic Effects

Most cancers in their earliest stages are asymptomatic but treatable if found. Most primary site cancers cause certain

symptoms that are recognizable causes for suspicion or concern. For example, endometrial cancer causes abnormal bleeding so often that it is usually detected in its early stages. Laryngeal cancer causes hoarseness, which is also an early sign. However, lung cancer is usually quite extensive before it causes enough symptoms to warrant investigation, as is true with breast cancer if it is a deeply buried tumor that is difficult to palpate. Most cancer is detected early and can be cured or successfully treated.

As the cancer progresses, symptoms characteristic of the involved organ or tissue may start to develop. With advanced cancer, nausea, vomiting, and retching (NVR) accompanied by anorexia and subsequent weight loss are common as a result of the malignant process and its treatment. NVR is especially prevalent in association with lung carcinoma, hypernephroma, and pancreatic carcinoma.

Anorexia has been attributed to tumor production of TNF, which is a protein (a cytokine) also called *cachectin*. TNFs are believed to play an important role in mediating inflammation and cytotoxic reactions (along with interleukins). TNFs produce necrosis of tumor cells by eliminating the blood supply to these growths. Small amounts of TNF are beneficial in promoting wound healing and preventing tumors, but uncontrolled production is accompanied by symptoms of fever, weight loss, and tissue damage that can cause more problems than the benefits provided.

Cancer-related anorexia/cachexia (CAC) is a complex phenomenon in which metabolic abnormalities, proinflammatory cytokines produced by the host immune system, circulating tumor-derived catabolic factors, decreased food intake, and possibly other unknown factors all contribute. Profound muscle loss is prominent in CAC syndrome as a result of decreased protein synthesis and abnormal muscle proteolysis.

Later, the rapid growth of the tumor encroaches on healthy tissue, causing destruction, necrosis, ulceration, and hemorrhage and producing many local and systemic effects. Pain may occur as a late symptom caused by infiltration, compression, or destruction of nerves. With advanced or stage IV cancer, the host presents systemically with muscular weakness, anemia, and coagulation disorders such as granulocyte and platelet abnormalities. See the section on Disorders of Hemostasis and Thrombocytopenia in Chapter 14.

Fever may be seen with cancer in the absence of infection and is produced either by white blood cells inducing a pyrogen (an agent that causes fever) or by direct tumor production of a pyrogen. Continued spread of the cancer may lead to gastrointestinal, pulmonary, or vascular obstruction. Secondary infections frequently occur as a result of the host's decreased immunity and can lead to death.

Other vital organs may be affected, such as the brain, in which increased intracranial pressure by tumor cells can cause strokelike symptoms. In addition to the local effects of tumor growth, cancer can produce systemic signs and symptoms that are not direct effects of either the tumor or its metastases (e.g., paraneoplastic syndromes or fever with renal cancer).

## Cancer Pain

### Overview

One of the most common symptoms of cancer is pain, affecting between 50% and 70% of clients in its early stages and 60% to 90% of clients in late stages of the disease. It is estimated that 1.1 million Americans experience cancer-related pain annually.<sup>29</sup> Alternately stated, pain occurs in approximately one-quarter of adults with newly diagnosed malignancies, one-third of individuals undergoing treatment, and three-quarters of all people with advanced disease.<sup>71,195</sup>

Depression and anxiety may increase the person's perception of pain or may be the result of the cancer pain. Symptoms often go unreported or underreported because clients are reluctant to take the pain medication prescribed. An unfounded fear of tolerance, addiction, or adverse effects from pain medication may result in under-reporting of painful symptoms with subsequent inadequate cancer pain control and unnecessary pain-induced loss of function. Likewise, physicians may hesitate to provide adequate pain medications based on this misconception of client addiction.

### Etiology and Pathogenesis

The cause of cancer pain is multifaceted, and the characteristics of the pain depend on the tissue structure, as well as on the mechanisms involved (Table 9-3). Some pain is caused by pressure on nerves or by the displacement of nerves. Microscopic infiltration of nerves by tumor cells can result in continuous, sharp, stabbing pain generally following the pattern of nerve distribution. Ischemic pain (throbbing) may also result from interference with blood supply or from blockage within hollow organs.

A common cause of cancer pain is metastasis of cancer to bone. Lung, breast, prostate, thyroid, and the lymphatics are the primary sites responsible for most metastatic bone disease. Bone metastasis results in increased release of prostaglandins and cytokines and subsequent bone

destruction caused by breakdown and resorption. Bone pain may be mild to intense. Movement, weight bearing, and ambulation exacerbate painful symptoms from bone destruction. Pathologic fractures with resultant muscle spasms can develop; in the case of vertebral involvement, nerve pain may also occur.

Pain may also result from diagnostic or therapeutic procedures such as surgery, radiation therapy, or chemotherapy (e.g., mucositis, stomatitis, esophageal inflammation, localized skin burns; see Table 9-8).

### Clinical Manifestations

Signs and symptoms accompanying mild-to-moderate superficial pain may include hypertension, tachycardia, and tachypnea (rapid, shallow breathing) as the result of a sympathetic nervous system response. In severe or visceral pain, a parasympathetic nervous system response is more characteristic, with hypotension, bradycardia, nausea, vomiting, tachypnea, weakness, or fainting.

Spinal cord compression from metastases may present as radicular back pain, leg weakness, and unilateral loss of bowel or bladder control. Back pain may precede the development of neurologic signs and symptoms. The presence of jaundice in association with an atypical presentation of back pain may indicate hepatobiliary obstruction and/or liver metastasis. Signs of nerve root compression may be the first indication of a cancer, in particular lymphoma, multiple myeloma, or cancer of the lung, breast, prostate, or kidney. Other neurologic or musculoskeletal manifestations of neoplasm are discussed in the section on Paraneoplastic Syndromes in this chapter.

Immobility and inflammation can lead to pain. Inflammation with its accompanying symptoms of redness, edema, pain, heat, and loss of function may progress to infection, necrosis, and sloughing of tissue. If the inflammatory process alone is present, the pain is characterized by tenderness. Pain may be excruciating in the presence of tissue necrosis and sloughing.

**Table 9-3** Common Patterns of Pain Referral

Pain Mechanism	Lesion Site	Referral Site
Somatic	C7, T1-T5 vertebrae	Interscapular area, posterior shoulder
	Shoulder	Neck, upper back
	L1, L2 vertebrae	SI joint and hip
	Hip joint	SI joint and knee
	Pharynx	Ipsilateral ear
	TMJ	Head, neck, heart
Visceral	Diaphragmatic irritation	Shoulder, lumbar spine
	Heart	Shoulder, neck, upper back, TMJ
	Urothelial tract	Back, inguinal region, anterior thigh, and genitalia
	Pancreas, liver, spleen, gallbladder	Shoulder, midthoracic or low back
	Peritoneal or abdominal cavity (inflammatory or infectious process)	Hip pain from abscess of psoas or obturator muscle
Neuropathic	Nerve or plexus	Anywhere in distribution of a peripheral nerve
	Nerve root	Anywhere in corresponding dermatome
	CNS	Anywhere in region of body innervated by damaged structure

From Goodman CC, Snyder TE: *Differential diagnosis for the physical therapist: screening for referral*, ed 4, Philadelphia, 2007, WB Saunders. SI, Sacroiliac; TMJ, temporomandibular joint; CNS, central nervous system.

## Pain Control

Pain management and control may depend on its underlying etiology. For example, epidural metastases with impending spinal cord compression require treatment with steroids, radiation, chemotherapy, or neurosurgery. Abdominal pain caused by obstruction of the hollow organs requires evaluation for surgical intervention.<sup>41</sup>

Treatment approaches depend on whether the individual is experiencing acute or chronic pain. The hope is to begin by gaining control of the pain during the acute phase and then to sustain that pain relief while minimizing side effects.

Pain should be screened, assessed, and managed according to clinical practice guidelines (CPGs). CPGs for the treatment of cancer-related pain in adults outlining the process of screening, evaluation, and intervention have been published by the National Comprehensive Cancer Network (NCCN).<sup>131</sup> A similar clinical practice guideline is available from the NCCN for pediatric cancer pain.<sup>135</sup>

Before starting therapy, the physician determines the underlying pain mechanism and diagnoses the pain syndrome. Pain control measures used include narcotic and nonnarcotic analgesics; chemotherapy or radiation therapy or both; surgery; nerve blocks; or other more invasive pain control measures, such as intraspinal opioids, rhizotomy, or cordotomy. Newer drugs, such as the bisphosphonates, have been useful in the treatment of refractory bone pain.<sup>29</sup>

Appropriate opioid selection may be difficult and depends on the individual's pain intensity and any current analgesic therapy. Morphine, hydromorphone, fentanyl, and oxycodone are the opioids commonly used in the United States. A balance between analgesia and side effects might be achieved by changing to an equivalent dose of an alternative opioid. This approach, known as *opioid rotation*, is now a widely accepted technique used to address poorly responsive pain.<sup>131</sup>

Several methods of continuous infusion that are widely used in clinical practice include "around the clock," "as needed," and "patient-controlled analgesia" (PCA). Around the clock dosing is provided to chronic pain patients for continuous pain relief. A "rescue dose" should be provided as a subsequent treatment for patients receiving these controlled-release medications. Rescue doses of short-acting opioids should be provided for pain that is not relieved by sustained/controlled release opioids.

Opioids administered on an as needed basis are for patients who have intermittent pain with pain-free intervals. The as needed method is also used when rapid dose escalation is required.

The PCA technique allows a person to control a device that delivers a bolus of analgesic "on demand" (according to and limited by parameters set by a physician). This system permits the person to self-administer a premeasured dose of analgesic by pressing a button that activates a pump syringe containing the analgesic. Small intermittent doses of the analgesic administered via intravenous (IV) line maintain blood levels that ensure comfort and minimize the risk of oversedation. Clinical studies report that people using PCA effectively maintain comfort

without oversedation and use less drug than the amount normally given by intramuscular (IM) injection.

Nonpharmacologic modalities, such as massage, acupuncture, imagery/hypnosis, reflexology, relaxation training, and other forms of complementary therapies, are based on client preference and clinical judgment of what is best when practicing integrative medicine or health care. Complementary therapies can lessen procedural pain and distress even among children, especially when fear, anxiety, and tension heighten pain perception.<sup>6,41,114</sup>

Whereas severe cancer pain is treated pharmaceutically, mild-to-moderate joint and muscle pain can be addressed by the rehabilitation professional. Pain elimination through the use of medication may not be possible without accompanying severe loss of function, which is an undesirable outcome.

Noninvasive physical agents, such as cryotherapy, thermotherapy, electrical stimulation, immobilization, exercise, massage, biofeedback, and relaxation techniques, may be effective in pain management. Much debate exists about the safety and efficacy of massage therapy for individuals with cancer, especially anyone with lymphedema or at risk for developing lymphedema.<sup>34</sup> A review of data included in the Cochrane Database of Systematic Reviews suggests that conventional care for people with cancer can safely incorporate massage therapy, although individuals with cancer may be at higher risk for adverse events. There is no evidence that massage therapy can spread cancer, although direct pressure over a tumor is usually discouraged.<sup>34</sup>

The strongest evidence for the benefits of massage is stress and anxiety reduction. Research regarding the use of massage for pain control and management of other symptoms is promising. Massage therapists may advocate the use of massage to reduce constipation, improve immune system function, help promote postoperative wound healing, and reduce scar tissue formation, as well as to help release metabolic waste by improving circulation. Published trials for these indications have not been reported.<sup>34</sup>

Modifications to massage (e.g., lighten pressure or avoid deep tissue massage) may be necessary to prevent potential harm such as bleeding, fracture, or increased pain when individuals with cancer receiving massage have a coagulation disorder (low platelet count or when receiving warfarin/heparin/aspirin therapy). Similar precautions are required for anyone with cancer metastases to the bones. Massage should be avoided over open or healing wounds or radiation dermatitis.<sup>34</sup>

People with cancer may also experience pain because of nerve damage. This damage can be caused directly by tumor invasion or indirectly as a side effect of cytotoxic drug therapy (e.g., taxanes or platinum agents). The treatment of neuropathic pain remains a dilemma since conventional analgesic drugs do not always provide relief.

Recommended treatment for neuropathic pain includes infrared (Anodyne), antidepressant drugs (e.g., amitriptyline); antiepileptics (e.g., carbamazepine and gabapentin); and steroids (e.g., methylprednisolone and dexamethasone). Pain relief is usually not immediate, and the drugs used must be taken continuously, thus side

effects, such as sedation and bone marrow depression, can be additional problems.<sup>29,84</sup>

Management of pain in people with cancer who live in long-term care facilities remains an ongoing concern. Consistent, daily pain is prevalent among nursing home residents with cancer and is frequently untreated, particularly among older and minority clients.<sup>16</sup> For individuals with difficult-to-control chronic pain, complementary therapies can help even if it is only to reduce the level of analgesics required to maintain pain control.

## Cancer-Related Fatigue

Much has been written about cancer-related fatigue (CRF) and its impact on clients. CRF is a distressing, persistent, and subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning.<sup>133</sup> CRF syndrome is a collection of symptoms with multiple characteristics and problems. Fatigue is a nearly universal symptom in all people receiving chemotherapy, radiotherapy, and treatment with biologic response modifiers; reduced physical performance and fatigue are universal after bone marrow transplantation.

Up to 30% of cancer survivors report a loss of energy for years after cessation of treatment. For many people with cancer, fatigue is severe and imposes limitations on normal daily activities.<sup>25</sup> Many people's perceptions are that fatigue is more distressing than pain or nausea and vomiting, which can be managed with medication for most clients.

Fatigue should be screened, assessed, and managed according to CPGs, which have been published for CRF.<sup>133</sup> All individuals should be screened for fatigue at their initial visit, at regular intervals during and after cancer treatment, and as clinically indicated. Fatigue should be recognized, evaluated, monitored, documented, and treated promptly for all age groups, at all stages of disease, during and after treatment. Clients and their families should be informed that management of fatigue is an integral part of total health care.<sup>133</sup>

Using a numeric rating scale, fatigue can be rated as mild (1 to 3), moderate (4 to 6), or severe (7 to 10).<sup>158,179</sup> Children can be asked if they are "tired" or "not tired." Fatigue that causes distress or interferes with daily activities or functioning should be treated according to its severity and the presence of other treatable factors known to contribute to fatigue (e.g., pain, emotional distress, sleep disturbance, anemia, nutritional deficits, deconditioning, and comorbidities).

Clients should be reassured that treatment-related fatigue is not necessarily an indicator of disease progression. It may be the result of anemia, deconditioning, or the presence of certain cytokines (e.g., interleukin [IL]-1, IL-6, or TNF-a). There may be contributing psychosocial factors such as anxiety, depression, and disrupted sleep pattern.

Despite the prevalence of CRF, the exact mechanisms involved in its pathophysiology are unknown. Abnormal accumulation of muscle metabolites, production of cytokines, changes in neuromuscular function, abnormalities in adenosine triphosphate (ATP) synthesis, serotonin

dysregulation, and vagal afferent activation are just a few more of the proposed theories. Comorbidities, such as cardiopulmonary impairments, may put an individual at greater risk for fatigue.<sup>133</sup>

Likewise, the cause of fatigue in posttreatment disease-free individuals is unclear and likely multifactorial. Higher serum markers, such as interleukin-1 receptor antagonist (IL-1ra) and soluble TNF type II (sTNF-RII), and lower Cortisol levels have been observed in fatigued cancer survivors compared with nonfatigued survivors. Significantly higher levels of circulating T lymphocytes have also been observed in fatigued survivors. These findings together point to a chronic inflammatory process involving T cells as a possible fatigue-inducing mechanism.<sup>133</sup>

## Paraneoplastic Syndromes

### Overview and Definition

In addition to the local effects of tumor growth, cancer can produce systemic signs and symptoms that are not direct effects of either the tumor or its metastases. When tumors produce signs and symptoms at a site distant from the tumor or its metastasized sites, these remote effects of malignancy are collectively referred to as *paraneoplastic syndromes*.

Although malignant cells frequently lose the function, appearance, and properties associated with the normal cells of the tissue of origin, they can acquire in some cases new cellular functions uncharacteristic of the originating tissue. Many of these syndromes involve ectopic hormone production by tumor cells or the secretion of biochemically active substances that cause metabolic abnormalities. For example, tumors in nonendocrine tissues sometimes acquire the ability to produce and secrete hormones that are distributed by the circulation and act on target organs at a site other than the location of the tumor. The most common cancer associated with paraneoplastic syndromes is small cell cancer of the lung, which can produce adrenocorticotrophic hormone (ACTH) in amounts sufficient to cause Cushing's syndrome.

Malignancy is often associated with a wide variety of musculoskeletal disorders, which may be the presenting symptoms of an occult tumor. Although musculoskeletal symptoms often result from direct invasion by the malignancy or its metastases into bone, joints, or soft tissue, they may also occur without invasion as a result of the paraneoplastic disorders, including well-recognized syndromes, as well as less well-defined disorders referred to as *cancer arthritis*.<sup>193</sup>

### Incidence

Previously, paraneoplastic syndromes occurred in 10% to 20% of all cancer clients, but this figure may be increasing because of greater physician awareness and the availability of serodiagnostic tests for some syndromes. Neurologic paraneoplastic syndromes are more rare, occurring in 1% to 2% of people with malignancy.

### Etiology and Pathogenesis

The causes of paraneoplastic syndromes are not well understood, but the following four groups of mechanisms have been identified:

**Table 9-4** Paraneoplastic Syndromes: Rheumatologic Associations and Clinical Features

Malignancy	Rheumatologic Associations	Clinical Features
Lung cancer	Myasthenic syndrome	Proximal leg weakness
Lymphoproliferative disease (leukemia)	Vasculitis	Necrotizing vasculitis
Plasma cell dyscrasia	Cryoglobulinemia	Vasculitis, Raynaud's disease, arthralgia, neurologic symptoms
Hodgkin's disease	Immune complex disease	Nephrotic syndrome
Ovarian cancer	Complex regional pain syndrome	Palmar fasciitis and polyarthritis
Carcinoid syndrome	Scleroderma	Scleroderma-like changes: anterior tibia
Colon cancer	Pyogenic arthritis	Enteric bacteria cultured from joint
Mesenchymal tumors	Osteogenic osteomalacia	Bone pain, stress fractures
Renal cell cancer (and other tumors)	Severe Raynaud's phenomenon	Digital necrosis
Pancreatic cancer	Panniculitis	Subcutaneous nodules, especially males
Lung cancer, small cell		Eaton-Lambert syndrome

**Table 9-5** Muscular and Cutaneous Disorders Associated with Malignancy

Muscular	Cutaneous
Amyloidosis	Acanthosis (diffuse thickening)
Amyotrophic lateral sclerosis	Dermatomyositis
Polymyositis	Extramammary Paget's disease
Lambert-Eaton myasthenic syndrome (LEMS)	Nigricans (blackish discoloration; changes in skin pigmentation)
Myasthenia gravis	Pemphigus vulgaris (water blisters)
Metabolic myopathies	Pruritus (itching)
Primary neuropathic diseases	Pyoderma gangrenosum (eruption of skin ulcers)
Type II muscle atrophy	Reactive erythemas (skin redness)

Data from Gilkeson GS, Caldwell DS: Rheumatologic associations with malignancy, *J Musculoskel Med* 7(1):70, 1990; Cohen PR: Cutaneous paraneoplastic syndromes, *Am Fam Physician* 50:1273-1282, 1994.

- Effects initiated by a variety of vasoactive tumor products (e.g., serotonin, histamine, catecholamines, prostaglandins, and vasoactive peptides), which usually occur in the small bowel and less commonly in the lung or stomach.
- Effects caused by the destruction of normal tissues by tumor, such as occurs when osteolytic skeletal metastases cause hypercalcemia.
- Effects caused by unknown mechanisms, such as unidentified tumor products or circulating immune complexes stimulated by the tumor (e.g., osteoarthropathy as a result of bronchogenic carcinoma).
- Effects caused by autoantibodies (antibodies directed against the host's tissue), for example, cancer cells produce antibodies that impair presynaptic calcium channel activity, hindering the release of the neurotransmitter acetylcholine, resulting in muscle weakness.

There is increasing evidence that many of the neurologic paraneoplastic syndromes appear to be an immune reaction against antigens shared by the cancer and the nervous system. The immune response is triggered by and directed against the tumor, which then cross-reacts with protein expressed by the peripheral or CNS. Consequently, any part of the nervous system can be affected.<sup>61,113</sup>

#### Clinical Manifestations

The paraneoplastic syndromes are of considerable clinical importance because they may accompany relatively

limited neoplastic growth and provide an early clue to the presence of certain types of cancer. Nonspecific symptoms, such as neurologic changes, anorexia, malaise, diarrhea, weight loss, and fever, may be the first clinical manifestations of a paraneoplastic syndrome. Even these types of nonspecific symptoms occur as a result of the production of specific biochemical products by the tumor itself.

Paraneoplastic syndromes with musculoskeletal manifestations are listed in Table 9-4. Gradual, progressive muscle weakness may develop over a period of weeks to months. The proximal muscles (especially of the pelvic girdle) are most likely to be involved; the weakness does stabilize. Reflexes of the involved extremities are present but diminished. Proximal leg weakness (Lambert-Eaton myasthenic syndrome) is most often associated with small cell carcinoma of the lung.

Muscular and cutaneous disorders associated with malignancy are presented in Table 9-5. Myositis may precede, follow, or arise concurrently with the malignancy and tends to occur most often in older people. Cutaneous paraneoplastic syndromes are a large group of dermatoses that may be associated with an internal malignancy.

There may be rheumatologic symptoms referred to as *carcinoma polyarthritis*. This condition can be differentiated from rheumatoid arthritis by the presence of asymmetric joint involvement, involvement of primarily the lower extremity (although symmetric involvement of the hands has been reported),<sup>193</sup> explosive onset, late age

of onset, and the presence of malignancy and arthritis together. Neurologic paraneoplastic syndromes are of unknown cause and include subacute cerebellar degeneration, amyotrophic lateral sclerosis, sensory or sensorimotor peripheral neuropathy, Guillain-Barre syndrome, myasthenia gravis, and the Lambert-Eaton myasthenic syndrome (LEMS).

Isolated cases of paraneoplastic stiff-person syndrome have been reported in association with small cell lung cancer, thymoma (thymus), melanoma, and breast adenocarcinoma.<sup>95,136,159</sup> Women are affected twice as often as men, most likely because of the association with breast cancer. Paraneoplastic stiff-person syndrome is characterized by progressive symptoms of neuropathy or myopathy with increased muscle tone and rigidity in the spine and lower extremities, especially the ankle dorsiflexors with loss of ankle motion.<sup>127</sup>

The disease may take years to manifest but in some individuals, symptoms develop over a period of weeks. The first symptom may be a persistent progressive stiffening of the back or leg that is triggered by sudden noise, touch, fatigue, or made worse by stress such as time pressure (e.g., hurrying to cross a street). Stiffness progresses to hypertonia, spasm, and then severe, painful rigidity. Walking becomes difficult, and the individual is at increased risk for unprotected falls (i.e., they fall like a tin soldier). Symptoms are greatly relieved during sleep.

Although rare, this condition has been encountered by therapists in an oncology practice. Stiff-person syndrome is normally associated with a viral cause, such as meningitis or encephalitis, but in the case of cancer-induced stiff-person syndrome, it is chemically induced by the tumor, classifying it as a paraneoplastic syndrome.<sup>95</sup> It is seen more often in clients with a history of diabetes and other autoimmune diseases (e.g., hyperthyroidism, hypothyroidism, or anemia).<sup>127</sup>

## MEDICAL MANAGEMENT

**DIAGNOSIS, TREATMENT, AND PROGNOSIS.** Serodiagnostic tests are available for some paraneoplastic syndromes, and characteristic abnormalities in magnetic resonance imaging (MRI) have been identified in association with neurologic paraneoplastic syndromes. Biochemical markers in urine provide specific monitoring of the response of bone metastases to treatment. This early diagnosis of paraneoplastic syndromes provides for prevention of tumor progression and subsequent problems such as bone pain, fracture, and hypercalcemia. In the case of cancer polyarthritis, the absence of rheumatoid nodules, absence of rheumatoid factor, and absence of family history of rheumatoid disease help in the diagnostic process.

Interestingly, paraneoplastic syndromes do not necessarily parallel the course of the disease but can be more related to the amount of antibody present rather than the amount of tumor volume. Some of the cutaneous paraneoplastic syndromes will respond to specific measures, such as systemic corticosteroid therapy, but for the most part, successful resolution requires eradication of the underlying malignancy.

Diagnosis of stiff-man syndrome is made by physical examination and immunocytochemistry methods dem-

onstrating the presence of anti-GAD (glutamic acid decarboxylase) autoantibodies in the blood. Diagnosis may be confirmed by a positive response to medications used to treat this condition (e.g., benzodiazepines).

## MEDICAL MANAGEMENT OF CANCER

### Prevention

The goal of *Healthy People 2010* is to reduce the number of new cancer cases, as well as the illness, disability, and death caused by cancer. Evidence suggests that several types of cancer can be prevented and that the prospects for surviving cancer continue to improve. The ACS estimates that half of all cancer deaths in the United States could be prevented if Americans adopted a healthier lifestyle and made better use of available screening tests. The ability to reduce cancer death rates depends in part on the existence and application of various types of resources.

First, the means to provide culturally and linguistically appropriate information on prevention, early detection, and treatment to the public and to health care professionals are essential. Second, mechanisms or systems must exist for providing people with access to state-of-the-art preventive services and treatment. Third, a mechanism for maintaining continued research progress and for fostering new research is essential. Personalized prevention may become a tool in the future thanks to desktop oncology in the postgenome era of research. Desktop oncology refers to the genomics data produced by high technology. Desktop oncology provides knowledge on demand to anyone regarding cancer-related biomarkers. Combining genetic screening for cancer predisposition in the general population and selecting individualized targeted chemoprevention may dramatically improve cancer rates in the future.<sup>97</sup>

Studying older adults who do not develop cancer may help identify the genetic changes associated with age-resistant protective mechanisms. Genetic information that can be used to improve disease prevention strategies is emerging for many cancers and may provide the foundation for improved effectiveness in clinical and preventive medicine services.

### Primary Prevention

Prevention is the first key to the management of cancer. Primary prevention may include screening to identify high-risk people and subsequent reduction or elimination of modifiable risk factors (e.g., tobacco use, diet high in unsaturated fats and low in fiber, sun or radiation exposure). Physical activity and weight control also can contribute to cancer prevention.

*Chemoprevention*, the use of agents to inhibit and reverse cancer, has focused on diet-derived agents. More than 40 promising agents and agent combinations (e.g., green and black tea phenols, lycopene, soy isoflavones, vitamins D and E, selenium, and calcium) are being evaluated clinically as chemopreventive agents for major cancer targets, including breast, prostate, colon, and lung

cancer.<sup>98</sup> In addition, low-dose aspirin intake and nonsteroidal antiinflammatory drug (NSAID) intake have shown promising results in the prevention of gastrointestinal cancers.

Research focusing on a *cancer vaccine* to wake up the immune system with a warning that cancer is present and stimulate an immune response against cancer cells is being investigated in clinical studies, although currently no known specific immunization prevents cancer in general. The most promising vaccines are for malignant melanoma and prostate cancer; vaccines for cancer viruses (human papillomavirus [HPV] associated with cervical cancer<sup>171</sup> and hepatitis B virus [HBV] associated with liver cancer) are already in use.<sup>62</sup>

The person's own tumor cells can be obtained during surgery, radiated to inactivate them, and then reinfused. This stimulates the immune system to react and make antibodies against these specific cells. The vaccine specifically evokes the activity of killer T cells to directly target and destroy tumors in all vaccine recipients. A vaccine given on an outpatient basis would be less dangerous than surgery and less toxic than other cancer treatments such as chemotherapy and radiation therapy.

### Secondary Prevention

Secondary prevention aimed at preventing morbidity and mortality uses early detection<sup>185</sup> and prompt treatment (Table 9-6). Some drugs, such as tamoxifen (Nolvadex), are used in both primary and secondary prevention of breast cancer. Tamoxifen has been approved by the Federal Drug Administration (FDA) as a preventive agent in women who have a high risk for possible development of breast cancer.<sup>211</sup> The preliminary results of a randomized trial comparing tamoxifen to a placebo in women considered at high risk for breast cancer suggested that the risk of breast cancer in this group of high-risk women could be decreased by approximately 50% with the administration of tamoxifen.<sup>141</sup>

Multifactor risk reduction is an important part of secondary prevention for people diagnosed with cancer at risk for recurrence. This is especially true because the adverse effect of several risk factors is cumulative and many risk factors are interrelated.

### Tertiary Prevention

Tertiary prevention focuses on managing symptoms, limiting complications, and preventing disability associated with cancer or its treatment.

## Diagnosis

Medical history and physical examination are usually followed by more specific diagnostic procedures. Useful tests for the early detection and staging of tumors include laboratory values, radiography, endoscopy, isotope scan, CT scan, mammography, MRI, and biopsy. Advances in nuclear medicine have made it possible to examine images of organs, structures, and physiologic or pathologic processes and detect the distribution of radiopharmaceuticals according to their uptake and metabolism.

### Tissue Biopsy

Biopsy of tissue samples is an important diagnostic tool in the study of tumors. Tissue for biopsy may be taken by curettage (Papanicolaou [Pap] smear), fluid aspiration (pleural effusion, lumbar puncture, or spinal tap), fine needle aspiration (breast or thyroid), dermal punch (skin or mouth), endoscopy (rectal polyps), or surgical excision (visceral tumors and nodes).

An *open biopsy* is performed in the operating room and consists of making an incision and removing a portion of the abnormal tissue. The amount removed depends on the abnormality, but it is usually a piece of tissue about one inch in diameter.

*Needle biopsy* uses a large diameter needle to take a core or plug of tissue. An incisional biopsy takes a slice or wedge of the lesion but does not attempt to remove the entire pathologic structure. Excisional biopsy (also referred to as a *lumpectomy*) removes the tumor and a perimeter of normal tissue or "margins." The goal is to remove enough tissue to get negative margins when the tissue sample is examined under a microscope by a pathologist.

*Stereotactic mammotome biopsy* of the breast uses digital x-rays of the breast taken from two angles to locate the abnormality seen on the mammogram. A computer then calculates the proper angle and depth of insertion of a core biopsy needle. This needle is inserted into the breast, using local anesthesia, and multiple (a dozen or more) core specimens are removed. Each core is about 2 mm by 15 mm long. These cores are then sent to the pathologist for diagnosis. A second type of stereotactic procedure places a wire into the exact location of an abnormality within the breast. Ultrasound or mammography is used to find the lesion. The surgeon uses the wire to relocate the abnormality within the breast during an open biopsy. The procedure for placing the wire is the same as for taking a core biopsy, but a thin needle is used instead of a core biopsy needle. Once the needle is in place, a thin wire is inserted through the needle, and the needle is removed.

*Sentinel lymph node (SLN) biopsy* has become a standard diagnostic procedure to assess lymph node status of various tumors (e.g., breast, melanoma, endometrial, valvular, or head and neck) and to assess staging. A blue dye is injected around the cancerous tumor (or the biopsy site if the tumor has been removed). The dye flows through the ducts, and the first node or nodes it reaches is identified as the sentinel or sentinels. An incision is made over the nodes, and the blue-stained sentinel node or nodes (1 to 3) are removed and analyzed. The removal of more than three SLNs is classified as a dissection. Complications of SLN biopsy include allergic reaction to the blue dye (less than 1%), pneumothorax from unintended opening of the parietal pleura, sensory or motor nerve injury (small risk), lymphedema, surgical site infections (less than 1%), and seromas (10%).<sup>76</sup>

Information on the lymphatic drainage from the cancer can have a direct impact on surgery. SLN biopsy has reduced the number of unnecessary axillary dissections in breast cancer. The status of axillary nodes is the most

**Table 9-6** Early Detection of Cancer

Cancer Site	Population	Test or Procedure	Frequency
Breast	Women, aged ≥20 years	Breast self-examination (BSE)	Beginning in their early 20s, women should be told about the benefits and limitations of BSE. Any new breast symptoms should be reported to a health professional. Women who choose to do BSE should receive instruction, and their techniques should be reviewed by a qualified health care professional. It is acceptable for women to choose not to do BSE or to do BSE irregularly.
		Clinical breast examination (CBE)	Women in their 20s and 30s should be part of a periodic health examination, preferably at least every 3 years. Asymptomatic women aged 40 years and over should continue to receive a CBE as part of a periodic health examination, preferably annually.
		Mammography	Begin annual mammography at age 40 years; CBE should be performed first.
Colorectal	Men and women, aged ≥50 years	Fecal occult blood test (FOBT) or fecal immunochemical test (FIT), or Flexible sigmoidoscopy, or FOBT and flexible sigmoidoscopy, or Double-contrast barium enema (DCBE), or Colonoscopy	Annual, starting at age 50 years. Every 5 years, starting at age 50 years. Annual FOBT (or FIT) and flexible sigmoidoscopy every 5 years, starting at age 50 years. DCBE every 5 years, starting at age 50 years. Colonoscopy every 10 years, starting at age 50 years.
	Men, age ≥50 years	Digital rectal examination (DRE) and prostate-specific antigen test (PSA)	The PSA test and the DRE should be offered annually, starting at age 50 years, for men who have a life expectancy of at least 10 more years.
Cervix	Women, age ≥18 years	Papanicolaou (Pap) test	Cervical cancer screening should be approximately 3 years after a woman begins having vaginal intercourse, but no later than 21 years of age. Screening should be done every year with conventional Pap tests or every 2 years using liquid-based Pap tests. At or after age 30 years, women who have had three normal test results in a row may get screened every 2 to 3 years with cervical cytology alone, or every 3 years with a human papillomavirus DNA test plus cervical cytology. Women age ≥70 years who have had three or more normal Pap tests and no abnormal Pap tests in the last 10 years and women who have had a total hysterectomy may choose to stop cervical cancer screening.
Endometrial	Women, at menopause	At the time of menopause, women at average risk should be informed about risks and symptoms of endometrial cancer and strongly encouraged to report any unexpected bleeding or spotting to their physicians.	
Cancer-related checkup	Men and women, age ≥20 years	On the occasion of a periodic health examination, the cancer-related checkup should include examination for cancers of the thyroid, testicles, ovaries, lymph nodes, oral cavity, and skin, as well as health counseling about tobacco, sun exposure, diet and nutrition, risk factors, sexual practices, and environmental and occupational exposures.	

Data from The American Cancer Society 2007. Available on-line at: <http://www.acs.org>.

important prognostic factor in breast cancer and in determining the medical management.

### Tumor Markers

Tumor markers, substances produced and secreted by tumor cells, may be found in the blood serum. The level of tumor marker seems to correlate with the extent of disease. A tumor marker is not diagnostic itself but can signal malignancies. Carcinoembryonic antigen (CEA) is one tumor marker that may indicate malignancy of the large bowel, stomach, pancreas, lungs, and breasts. CEA and other serum titers, such as CA 125 (ovarian), CA 27-29 (breast), and prostate-specific antigen (PSA), may be valuable during chemotherapy to evaluate the extent of response and detect tumor recurrence.

Other tumor markers found in the blood (no more specific than CEA) include alpha fetoprotein (AFP), a fetal antigen uncommon in adults and suggestive of testicular cancer. The beta-2 (p<sub>1</sub>) microglobin is used in the monitoring of lymphomas, and lactic dehydrogenase (LDH) is particularly elevated in fast-growing malignancies. Human chorionic gonadotropin (P subunit) may indicate testicular cancer or choriocarcinoma. PSA helps evaluate prostatic cancer. Because of the lack of specificity of the markers individually (except PSA), test panels are used more frequently rather than just individual tumor marker evaluations.<sup>135</sup>

Several research institutes have developed a monoclonal antibody that identifies breast cancer and other cancer cells. The monoclonal antibody is used to devise a simple blood test for use in diagnosis and monitoring treatment of breast and ovarian cancers and will be used in the future to diagnose colon cancer. Combining the breast cancer antibody with nuclear medicine scanning techniques will provide a noninvasive means of determining lymphatic spread and guide surgeons in determining the extent of surgery required.<sup>10</sup>

## Treatment

Changes in the health care system have shifted much of cancer care to the ambulatory and home settings. The medical management of cancer may be curative (i.e., with the intent to cure) or palliative (i.e., provides symptomatic relief but does not cure). Major therapies that are the focus of curative cancer treatment at this time include surgery, radiation, chemotherapy, biotherapy (also called immunotherapy or molecularly based therapy), angiogenesis therapy, and hormonal therapy.

New tests called *gene profiling assays* are now available that can predict fairly accurately what certain tumors will do and how best to treat them. Research has shown that tumors, like any other living tissue, contain genetic information that can be read with increasing accuracy. The goal is to analyze the genetic makeup of the tumor then choose the specific treatment most likely to be effective given that gene profile, while avoiding exposing the person to toxic therapies that might not be helpful or necessary. Two gene-profiling tests are already available for breast cancer; others are being evaluated for non-Hodgkin's lymphoma, head and neck cancer, prostate cancer, kidney cancer, melanoma, and ovarian cancer.

Many cancers, such as myelodysplasia and hematologic malignancies (e.g., lymphoma, myeloma, leukemia), can be treated effectively in older adults, although advanced age does present many challenges. The future of oncologic care may rest on the model of individualized (tailored) therapy based on a pretreatment assessment of the each individual's organ reserves, physical condition, and cognitive function. Identifying predictive factors of successful outcome will help assess who could benefit from more aggressive treatment and have the greatest chance for successful outcomes.<sup>13,52</sup> When curative measures are no longer possible or available, palliative treatment may include radiation, chemotherapy, physical therapy (e.g., physical agents, exercise, positioning, relaxation techniques, biofeedback, or manual therapy), medications, acupuncture, chiropractic care, alternative medicine (e.g., homeopathic and naturopathic treatment), and hospice care.

### Complementary and Alternative Medicine

Many people are seeking help in the cure and palliation of cancer through complementary and alternative medicine (CAM) therapies, such as acupuncture, hypnosis, mind-body techniques, massage, music, yoga, meditation, and other methods, to improve physical and mental well-being.<sup>5,41</sup> Conventional treatments do not always relieve symptoms of pain, fatigue, anxiety, and mood disturbance. Some people cannot tolerate the side effects of conventional treatment. CAM has received consumer attention and concern on the part of those who provide conventional or standard medical therapy.

The ACS has published a guide to help consumers make these kinds of treatment decisions<sup>5</sup> and provided some direction for health care professionals.<sup>203</sup> Major research institutions and universities are beginning to investigate the effectiveness of these types of interventions for cancer. A new movement toward integrative medicine combining the best of complementary modalities with mainstream conventional therapies has been launched.

### Major Treatment Modalities

Cancer treatment depends on an understanding of the biology of metastasis and how tumor cells interact with the microenvironment of different organs to design effective therapies.<sup>56</sup> Each of the curative therapies described here may be used alone or in combination, depending on the type, stage, localization, and responsiveness of the tumor and on limitations imposed by the person's clinical status.

*Surgery*, once a mainstay of cancer treatment, is now used most often in combination with other therapies. Surgery may be used curatively for tumor biopsy and tumor removal or palliatively to relieve pain, correct obstruction, or alleviate pressure. Surgery can be curative in persons with localized cancer, but 70% of clients have evidence of micrometastases at the time of diagnosis, requiring surgery in combination with other treatment modalities to achieve better response rates. Adjuvant therapy used after surgery eradicates any residual cells.

**Radiation Therapy.** Radiation therapy (RT or XRT), also known as radiotherapy, plays a vital role in the

multimodal treatment of cancer. It is used to destroy the dividing cancer cells by destroying hydrogen bonds between DNA strands within the cancer cells, while damaging resting normal cells as little as possible. Recent advances in RT have primarily involved improvements in dose delivery. The focus of future treatment is on combining RT with targeted therapies such as angiogenesis inhibitors.<sup>31</sup>

Radiation consists of two types: ionizing radiation and particle radiation. Both types have the cellular DNA as their target; however, particle radiation produces less skin damage. The goal is to ablate as many cancer cells as possible while simultaneously sparing surrounding normal tissues. Radiation is given over a period of weeks to capture cells at each stage of the cell cycle. Radiation is particularly effective at the end of the G2 phase (Fig. 9-3) when the cells are most susceptible to radiation.

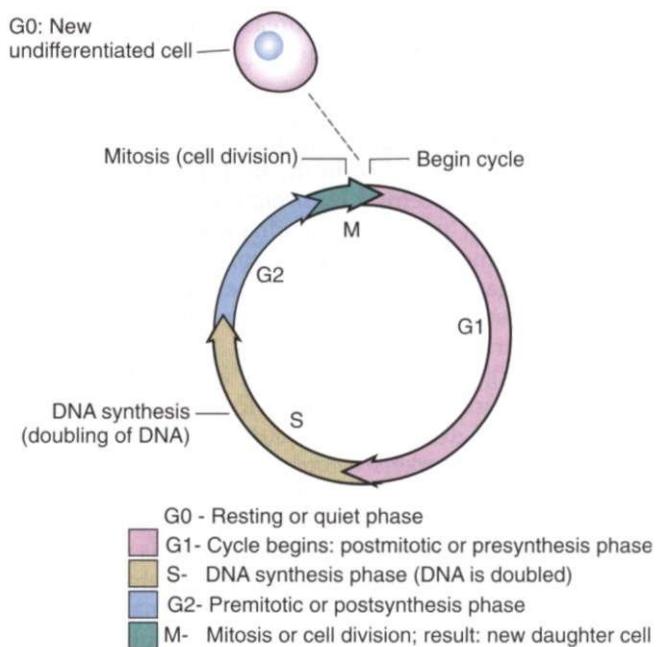
Radiation treatment approaches include external beam radiation and intracavitary and interstitial implants. Radiation may be used preoperatively to shrink a tumor, making it operable while preventing further spread of the disease during surgery. After the surgical wound heals, postoperative doses prevent residual cancer cells from multiplying or metastasizing.

RT may be delivered externally or internally depending on the type and extent of the tumor by (1) external beam (teletherapy), (2) sealed source (brachytherapy), and (3) unsealed source (systemic therapy). When the distance between the radiation source and the target is short, the term *brachytherapy* is used. Brachytherapy allows for a rapid falloff in dose away from the target volume. When the radiation source is at a distance from the target, the term *teletherapy* is used. Teletherapy allows for a more uniform dose across the target volume.

Modern radiology has advanced to include site-specific techniques that take into account complex tissue contours and irregular shapes, visceral movement, digestion, and the effect of respiration on the lungs when the lungs are the target organ. Intensity modulated RT (IMRT) now allows for sculpting the radiation field and dose to match the area being irradiated. Computer optimization techniques help determine the distribution of beam intensities across a treatment volume.<sup>20</sup>

X-rays, radioactive elements, and radioactive isotopes are most often used in RT. Isotopes implanted in the tumor or a body cavity by external beam sources are delivered in the form of electromagnetic waves (e.g., x-rays or gamma rays) or as streams of particles (e.g., electrons). X-rays generated by linear accelerators and gamma rays generated by radioactive isotopes (e.g., cobalt-60, radium-226, or cesium-137) are referred to as sealed source radiation therapies or brachytherapy. This form of radiation is used for the treatment of visceral tumors because the rays penetrate to great depths before reaching full intensity and thereby spare the skin from toxic effects.

Strontium and yttrium aluminum garnet (YAG) lasers have been administered for the palliation of bone pain related to metastatic bone disease in both prostate and breast cancer.<sup>102,192</sup> Electron beam irradiation is most useful in the treatment of superficial tumors, since energy



**Figure 9-3**

Cell cycle. One round of cell division requires duplication of DNA during the S phase and proper segregation of duplicated chromosomes during mitosis (M phase). G0 are the "resting cells" temporarily out of the proliferative cycle; when stimulated, these cells move into the G1 phase and begin to multiply. G1 and G2 are "gap" phases. G1 is the postmitotic period during which time RNA/protein synthesis occurs. G2 is the premitotic period and the last step in the mitotic cycle followed by M [mitosis] when cell division takes place. Most organ cells that are hormonally linked take approximately 19 to 33 days to complete one full cycle. Chemotherapy eliminates up to 95% of cancerous cells in the body; this is called the "kill rate." Not all cancer cells will be eradicated; the immune system may be able to eliminate the remaining cells but not always. Adjuvant treatment, such as chemotherapy and radiation therapy, is administered in repeated doses over time in an attempt to kill cells in the most susceptible phases. For example, chemotherapy is most effective during DNA synthesis and mitosis. Cells are most sensitive to radiation therapy in the G2 phase. A certain percentage of cells will be unaffected because they are in the G0 or resting phase. Cells in the G0 phase are undifferentiated or stem (mesenchymal) cells waiting until called on by the body to serve a particular (differentiated) need. Stem cells in the G0 phase are resistant to chemotherapy and radiation therapy and the reason chemotherapy and radiation therapy are not 100% effective modalities in the ablation of microcirculation of tumor cells. The repeated or cyclical treatment is designed to catch G0 cells later in the growth cycle. (Modified from Abeloff MD, Armitage JO, Niedrhuber JE, et al: *Clinical oncology*, ed 3, 2004, London, Churchill Livingstone.)

is deposited at the skin and quickly dissipates, sparing the deeper tissues from toxic effects.

Normal and malignant cells respond to radiation differently, depending on blood supply, oxygen saturation, previous irradiation, and immune status. Cells most affected by chemotherapy and radiation have the greatest oxygenation and are the fast producing cells (e.g., hair, skin). Generally, normal cells recover from radiation faster than malignant cells; damaged cancer cells cannot self-repair. Success of the treatment and damage to normal tissue also vary with the intensity of the radiation.

Standard radiation fractionation is a course of 1.8 to 2.0 Gy per day in single daily doses. Accelerated or hypo-

**Table 9-7** Major Chemotherapeutic Agents

Agent	Example	Action
Alkytating agents	Busulfan (myleran) Carmustine Chlorambucil (Leukeran) Cisplatin (Platinol) Cyclophosphamide (Cytoxan) Dacarbazine	Inhibit cell growth and division by directly attacking DNA; used most often in the treatment of chronic leukemias, Hodgkin's disease, lymphomas, some carcinomas of the lung, breast, prostate, and ovary.
Nitrosourea	Carmustine Lomustine Semustine	Similar to alkylating agents; inhibits changes necessary for DNA repair; crosses the blood-brain barrier, thus used to treat brain tumors, lymphomas, multiple myeloma, and malignant melanoma.
Antimetabolites	Cytarabine Decitabine Etoposide Fluorouracil (5-FU) Methotrexate Mercaptopurine (6-MP) Paclitaxel (Taxol)	Block cell growth by interfering with DNA synthesis during the S phase of the cell cycle; used to treat acute and chronic leukemias, choriocarcinoma, and some tumors of the GI tract, breast, and ovary.
Antitumor antibiotics	Bevacizumab (Avastin) Bleomycin (Blenoxane) Cetuximab (Erbitux) Dactinomycin Daunorubicin (DaunoXome) Doxorubicin (Adriamycin) Mitomycin (Mutamycin) Trastuzumab (Herceptin)	Inhibit cell growth by binding with DNA and interfering with DNA-dependent RNA synthesis; used with a variety of cancers.
Plant alkaloids	Paclitaxel (Taxol) Vinblastine Vincristine	Prevent cellular reproduction by disrupting cell mitosis; used to treat acute lymphoblastic leukemia, Hodgkin's and non-Hodgkin's lymphomas, neuroblastomas, Wilms' tumor, and some cancers of the lung, breast, and testes
Steroid hormones	Dehydroepiandrosterone (DHEA) Dexamethasone Tamoxifen	Prevents cell division and further growth of hormone-dependent tumor; does not directly kill cells so is not curative.

fractionation refers to delivering the same total dose over a shortened treatment time (one or just a few treatment sessions). Hyperfractionation refers to the same total delivered dose over the same treatment time but in an increased number of fractions; in other words, smaller fractions are delivered more often than once a day. Although a large single dose of radiation has greater cellular effects than fractions of the same amount delivered sequentially, a protracted schedule allows time for normal tissue to recover in the intervals between individual sub-lethal doses.<sup>20</sup>

Challenges with radiation treatment still remain because of the inability to identify microscopic disease with accuracy. Immobilizing patients and keeping them completely still for the duration of treatment is also difficult. Weight loss associated with treatment alters body geometry, requiring further corrections in dosimetry.

The next step in radiation oncology is to account for physiologic movements during irradiation. This may be accomplished with adaptive radiation with daily modulation of prescription and delivery using real-time imaging called four-dimensional (4-D) conformal RT (CRT).<sup>20</sup> See Chapter 5 for a more complete discussion of the effects of RT.

**Chemotherapy.** Chemotherapy includes a wide array of chemical agents to destroy cancer cells. It is particularly useful in the treatment of widespread or metastatic

disease, whereas radiation is more useful for treatment of localized lesions. Chemotherapy is used in eradicating residual disease, as well as inducing long remissions and cures, especially in children with childhood leukemia and adults with Hodgkin's disease or testicular cancer. Several major chemotherapeutic agents are listed in Table 9-7. For a more complete discussion of chemotherapy, see Chapter 5.

Chemotherapy (and RT) kills most of the billion or more cells in each cubic centimeter of tumor tissue. However, cytotoxic therapies do not always eradicate every tumor cell for several reasons. Unlike normal cells, cancer cells are genetically unstable and replicate inaccurately. As the tumor grows, multiple subpopulations of cells with different biologic characteristics develop. Some of the cells will be resistant to treatment. After the treatment-sensitive cells are eliminated, the resistant cells may divide rapidly, recreating a tumor that is now resistant to the therapy.<sup>194</sup>

Almost all chemotherapy agents kill cancer cells by affecting DNA synthesis or function, a process that occurs through the cell cycle. Each drug varies in the way this occurs within the cell cycle. Chemotherapy interferes with the synthesis or function of nucleic acid targeting cells in the growth phase and therefore does not kill all cells (e.g., 5% are in the quiet or quiescent phase and are unaffected by chemotherapy) (see Fig. 9-3).

Combination therapies are often used because some drugs work better during different cell cycles. For example antimetabolites are most effective during the presynaptic (G1) phase, whereas alkylating agents target cells during the synthesis of DNA (S phase) and the postsynthesis (G2) phase. Treatment is designed to capture cell cycles at different phases for optimum cell death.<sup>119</sup>

Chemotherapeutic drugs can be given orally, subcutaneously, intramuscularly (IM), intravenously (IV), intracavarily (into a body cavity such as the thoracic, abdominal, or pelvic cavity), intrathecally (through the sheath of a structure, such as through the sheath of the spinal cord into the subarachnoid space), and by arterial infusion, depending on the drug and its pharmacologic action and on tumor location. Administration in any form is usually intermittent to allow for bone marrow recovery between doses.

Although the effects of cancer treatment from chemotherapy, radiation therapy, hormonal therapy, and biotherapy are discussed in Chapter 5, new information about "chemobrain" has been published and updated here. Chemobrain, sometimes called "chemo fog" or "brain fog" refers to problems with memory, attention, and concentration reported by many people who have been treated with chemotherapy.

Not all chemotherapy recipients develop problems with cognitive or mental function but if it does happen, the effects can last several years. MRIs of brain structures have shown temporary shrinkage in the brain structures that are responsible for cognition and awareness. Shrinkage may be a possible physiologic explanation for chemotherapy-related cognitive difficulties.<sup>91</sup>

Three cancer drugs in particular (cisplatin, carmustine, cytosine arabinoside) have been implicated in laboratory cell cultures with killing brain cells. In fact 70% to 100% of brain cells compared to only 40% to 80% of cancer cells were destroyed by these drugs in animal studies. These cancer drugs may block new cell formation in the hippocampus, a brain structure essential to memory and learning.<sup>50</sup>

**Mediating the Effects of Chemotherapy.** Colony-stimulating factors (CSFs) may be used to support the person with low blood counts related to chemotherapy. CSFs function primarily as hematopoietic growth factors, guiding the division and differentiation of bone marrow stem cells. They also influence the functioning of mature lymphocytes, monocytes, macrophages, and neutrophils.

Currently, erythropoietin (EPO), human granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and thrombopoietin (oprelvekin) and various interleukins are being used for chemotherapy-induced pancytopenia (deficiency of all cellular components of blood). EPO is used to treat anemia by stimulating bone marrow production of red blood cells. Interleukins are a large group of cytokines sometimes called *lymphokines* when produced by the T-lymphocytes or *monokines* when produced by mononuclear phagocytes. Interleukins have a variety of effects, but most interleukins direct other cells to divide and differentiate. Both G-CSF and GM-CSF are very useful in protecting individuals from prolonged neutrophil nadirs

(lowest points after neutrophil count has been depressed by chemotherapy). Thrombopoietin (oprelvekin) has been recently identified and has shown promise in promoting elevation in platelet counts.<sup>169</sup> In addition, GM-CSF has shown significant antitumor effects that prolong survival and disease-free survival in adults with stage III and IV melanoma who are at high risk for recurrence after surgical resection.<sup>190</sup>

**Biotherapy.** Biotherapy, sometimes referred to as *immunotherapy* or *immune-based therapy*, relies on biologic response modifiers (BRMs) to change or modify the relationship between the tumor and host by strengthening the host's biologic response to tumor cells. Much of the work related to BRMs is still experimental, so the availability of this type of treatment varies regionally within the United States.

The most widely used agents include interferons, which have a direct antitumor effect, and IL-2, one type of cytokine, a protein released by macrophages to trigger the immune response.<sup>81</sup> In addition to their desired immune effects, interferons cause a number of significant toxicities, including constitutional, hematologic, hepatic, and prominent effects on the nervous system, especially depression.

Other forms of biotherapy include bone marrow or stem cell transplantation, monoclonal antibodies, CSFs, and hormonal therapy. Bone marrow transplantation (BMT) or peripheral stem cell transplantation (PSCT) is used for cancers that are responsive to high doses of chemotherapy or radiation. These high doses kill cancer cells but are also toxic to bone marrow; BMT provides a method for rescuing people from bone marrow destruction while allowing higher doses of chemotherapy for a better antitumor result.

BMT was a technique developed to restore the marrow to people who had lethal injury to that site because of bone marrow failure, destruction of bone marrow by disease, or intensive chemical or radiation exposure. At first, the source of the transplant was the marrow cells of a healthy donor who had the same tissue type (human leukocyte antigen [HLA]; markers on the white blood cells) as the recipient (usually a sibling or close family relative). Donor programs have been established to identify unrelated donors who have a matching HLA.

The transplant product is a very small fraction of the marrow cells called *stem cells*. These cells occur in the bone marrow and also circulate in the blood and can be harvested from the blood of a donor by treating the donor with an agent or agents (e.g., G-CSF) that cause a release of larger numbers of stem cells into the blood and collect them by hemapheresis. Since blood (peripheral site), as well as marrow, is a good source of cells for transplantation, the term *stem cell transplantation* has replaced the general term for these procedures (see the section on Bone Marrow Transplantation in Chapter 21).

Other immune-based strategies currently being evaluated or cancer therapy in preclinical models and clinical trials include vaccines combined with local therapies, the use of antioxidants during radiation therapy, and monoclonal antibodies (mAbs). mAbs are laboratory-engineered copies of proteins produced from a single

clone (monoclonal) of B-lymphocytes that can stimulate the immune system to attack cancer cells. mAbs are antibodies that are identical because they were produced by one type of immune cell and are all clones of a single parent cell.

These antibodies are biologic therapies that act specifically against a particular antigen. They can also be bound with radioisotopes and injected into the body to detect cancer by attaching to tumor cells. The antibody may not actually kill target cells, but rather it marks the cells so that other components in the immune system attack it or initiate a signaling mechanism that leads to the target cell's self-destruction.<sup>181</sup> Monoclonal antibodies have been developed to help combat specific cancers, including colorectal cancer and some forms of non-Hodgkin's lymphoma.

Research is under way to find a way to use these antibodies as a means of destroying specific cancer cells without disturbing healthy cells. Rituximab (Rituxan), trastuzumab (Herceptin), Alemtuzumab (Campath-1H), and Cetuximab (Erbitux) are a few of the monoclonal antibodies currently in use for cancer treatment (e.g., lymphoma, breast, colorectal, chronic leukemia, and head and neck cancer).

Avastin (bevacizumab, formerly known as anti-VEGF) is an antibody used in combination with chemotherapy in the treatment of colon, lung, and breast cancer. This antibody binds to vascular endothelial growth factor (VEGF) made by the tumor cells and prevents it from forming new blood vessels to supply the tumor cells.

Rituximab is used primarily in the treatment of non-Hodgkin's lymphoma. Rituximab binds to lymphoid cells in the thymus, spleen, lymph nodes, and peripheral blood in order to lyse and destroy specific immune target cells.

Trastuzumab is used in the treatment of metastatic breast cancer in women who have overexpression of the human epidermal growth factor receptor 2 (HER2) protein. It binds with this protein and inhibits proliferation of cells with this protein and also mediates an antibody-mediated destruction of the cancer cells that have the HER2 receptor overexpression.<sup>64</sup> Both agents are usually used in combination with or in addition to other chemotherapeutic agents for treatment.

Not all people respond to mAbs, presumably because of differences in the receptors being targeted. Molecular testing will have to become part of designer biologic therapy in which drugs are chosen on an individual basis after genetic profiling and immunoassay. Antibodies also function as carriers of cytotoxic substances, such as radioisotopes, drugs, and toxins, making them a key focus area of cancer research right now.<sup>181</sup>

**Antiangiogenic Therapy.** Antiangiogenic therapy shows promise as a strategy for cancer treatment. Research has shown that the one common area of vulnerability of all cells in any phase of growth is the nonnegotiable need for oxygen. Tumor cells cannot survive without oxygen and other nutrients transported by the blood. In fact, tumor cells cannot survive at distances greater than 150 μm from a blood vessel.<sup>194</sup>

Antiangiogenic therapy may be able to put a stop to pathologic angiogenesis, the process by which a malig-

nant tumor develops new vessels and is the primary means by which cancer cells spread. Antiangiogenesis factors, their receptors, and the signaling pathways that govern angiogenesis in solid tumors have been discovered. Treatment with antiangiogenesis factors (e.g., endostatin, angiostatin, or calpastatin) approved for use in the United States focuses on blocking the general process of tumor growth by cutting off their blood supply rather than on the destruction of an already formed cancerous mass.<sup>59</sup> Scientists expect that combinations of angiogenesis inhibitors or broad-spectrum angiogenesis inhibitors will be needed for long-term use in cancer if tumor cells have or develop multiple molecular signaling pathways, a characteristic called *redundancy*.<sup>60</sup>

In the future, antiangiogenic agents may be used as maintenance therapy to control cancer much the same way that medications are used to control hypertension or hyperlipidemia. It is expected that different mutations in cancer will require individualized therapy based on current knowledge of specific tumors, their patterns of resistance, and response to angiogenesis inhibitors.<sup>62</sup>

**Hormonal Therapy.** Hormonal therapy is used for certain types of cancer shown to be affected by specific hormones. For example, tamoxifen, an antiestrogen hormonal agent, is used in breast cancer to block estrogen receptors in breast tumor cells that require estrogen to thrive.

The luteinizing-releasing hormone leuprolide is now used to treat prostate cancer. With long-term use, this hormone inhibits testosterone release and tumor growth. Goserelin acetate (Zoladex) is a newer hormone used in prostate cancer that is a synthetic form of luteinizing hormone-releasing hormone (LH-RH). Goserelin acetate inhibits pituitary gonadotropic secretion, thus decreasing serum testosterone levels.<sup>211</sup>

### Effects of Cancer Treatment

Although it may make more sense to include a discussion of the side effects of cancer treatment in this chapter, we have opted to place that topic in Chapter 5 to help emphasize the point that the long-term effects of cancer treatment are problems that affect multiple systems. The therapist must take this approach when planning intervention and offering patient/client education.

With improved survival rates, we expect to see more delayed reactions and long-term sequelae to today's cancer treatment modalities. With improved survival and longevity, we may see an increased prevalence of cancer recurrence in the future, too. This may mean worsening of symptoms such as peripheral neuropathy or lymphedema from second and third rounds of treatment. In time, with the identification of genetic traits of cancer, treatment may become more specific to the cancer cells and less toxic to healthy cells and tissue, eventually reducing and maybe even eliminating side effects experienced by many of today's cancer survivors.

### Prognosis

Thirty years ago a cancer diagnosis was often a death sentence; survivors referred to themselves as "victims." Cancer is no longer considered a death sentence, and many survivors return to the mainstream of family life,

community activities, and work. Medical treatment is often provided in outpatient settings, making it possible to work during treatment.<sup>55</sup>

Today, there are 10 million cancer survivors in the United States; 65% of all people diagnosed with cancer have a 5-year survival rate. In general, this means that the chance of a person recently diagnosed with cancer being alive in 5 years is 65% of the chance of someone not diagnosed with cancer. Such statistics adjust for normal life expectancy (accounting for factors such as diabetes, heart disease, injuries, or dying of old age).<sup>5</sup>

In general, increased survival rates occur with screening and early detection, especially for cancers that do not have a highly effective treatment such as melanoma. Prognosis is influenced by the type of cancer, the stage and grade of disease at diagnosis, the availability of effective treatment, the response to treatment, and other factors related to lifestyle such as smoking, alcohol consumption, diet, and nutrition. Despite advances in early diagnosis, surgical techniques, systemic therapies, and patient care, the major cause of death from cancer is due to metastases that are resistant to therapy.<sup>56</sup>

The prognosis is poor for anyone with advanced, disseminated cancer. Researchers continue to search for the mechanisms responsible for cancer metastases and chemotherapeutic failure and develop new strategies to circumvent drug resistance. Generally, the earlier cancers are found, the simpler treatment may be and the greater likelihood of a cure.

The term *no evidence of disease* (NED) may be used when all signs of the disease have disappeared after treatment but before the end of 5 years occurs. There are no signs of the disease using current tests. If the response is maintained for a long period, the term *durable remission* may be used (Box 9-4). The person who is alive and without evidence of disease for at least 5 years after diagnosis is considered cured. The terms *survival* and *cure* do not always portray the functional status of a cancer survivor. Many people considered cured are left with physical limitations and movement dysfunctions that interfere with their daily lives.

Even without complete remission, cancer can be controlled to provide longer survival time and improved QOL, but these factors are not reflected in survival rates. Cancer statistics reported usually include a lag time so that rates may not reflect the most recent treatment advances. Survival rates for many cancers have increased from 1960 to the present, but not all cancers have been characterized by this increase. For example, while survival rates for Hodgkin's disease and prostate, testicular, and bladder cancers have increased by at least 25%, the survival rates for cancers of the oral cavity and pharynx, liver, pancreas, esophagus, and colon have decreased or increased less than 5% during the same period.

A significantly lower survival rate in black American men for most cancer classifications has been noted. This difference may be due to a variety of factors, including limited access to health care, little or no insurance, lack of a primary health care provider, limited knowledge of the benefits of early diagnosis and treatment, and greater exposure to carcinogens. Central to these social forces is

#### Box 9-4

#### DEFINITIONS OF CANCER TREATMENT OUTCOMES

##### Cure

- The disease is gone and there is no sign of it reappearing; individual must be in complete remission for at least 5 years (or more) from the time of treatment to be considered "cured."
- Cancer recurrence or the onset of a new type of cancer is still possible; in theory the chances of cancer recurrence or new cancer for a person who has been cured are no higher than someone who has not had cancer.

##### Complete Remission (CR)

- All signs of disease have disappeared after treatment although this does not mean there are no cancer cells present and it does not mean the person is cured. CR may be referred to as no evidence of disease (NED). After several years, this state may be referred to as durable remission until 5 years have passed and the individual is considered cured.

##### Partial Remission (PR)

- Primary tumor has been reduced to  $\frac{1}{2}$  its original size after treatment; also known as partial response.

##### Improvement

- Primary tumor has been reduced but remains more than  $\frac{1}{2}$  its original size.

##### Advanced Disease

- Disease has spread to more than one location; staging is used to describe the extent of disease.

##### Stable Disease

- No change with treatment; the cancer is not increasing or decreasing in size, extent, severity, or symptoms.

##### Refractory

- Cancer is resistant, does not respond to treatment, and continues to progress; also referred to as treatment failure, resistant cancer, or disease progression.
- Relapse.
- Cancer returns after treatment or a period of improvement either to the first place it started or in another place.

##### Survival Rate

- The percentage of people in a study or treatment group who are alive for a given period of time after diagnosis. This is commonly expressed as 1-year or 5-year survival rate referring to the chances of being alive in 1-year, 5-year, or 10-year increments compared to the chances of someone who has not been diagnosed with cancer.

##### Prognostic Index

- Used as a measure of risk for relapse, the prognostic index is not a predictor for death.

access to health care, including prevention, information, early detection, and quality treatment.<sup>212</sup>

In terminally ill individuals, rates of change are more important indicators of survival than absolute measures. Using a modified Barthel Index comprised of 10 activities of daily living (ADLs), each with five levels of dependency (maximum score more than 100 points), can

provide important predictions about length of time until death. Half of those individuals with advanced cancer who lose 10 or more points per week die within 2 weeks, and three-fourths are dead at 3 weeks. In contrast, 50% of all cases without declines in score survive for 2 months or more. This may be a useful tool for planning and end-of-life issues in a hospice setting.<sup>15</sup>

Selected older adults with cancer can benefit from intensive care. Age is associated with higher mortality, especially for adults over 60 years old and when combined with multiple comorbidities.<sup>188</sup> A comprehensive geriatric assessment can be helpful in identifying individuals likely to benefit from cytotoxic treatment. Therapies may be adjusted based on renal and cardiac function. Cardiac toxicity and neurotoxicity are common in persons aged 65 years and older.<sup>13</sup>

cancer clients. Some rehabilitation departments receive a copy of the daily operating room schedules. Patients are targeted ahead of time for immediate postoperative consultation with a physical therapist.

Therapists need to advocate as a group that all patients see a physical therapist after lymph node dissection. Many experts in the field of cancer treatment suggest automatic referral to a physical therapist once the diagnosis of cancer has been made—rather than waiting until radiation-induced fibrosis causes disabling contractures, for example. The truth probably lies somewhere in between; more evidence is needed to identify people at risk for poor outcomes that could be improved with physical therapy and predictive factors supporting the need for physical therapy intervention.

Psychosocial-spiritual issues (e.g., loss, grief, and anger) and client diversity (e.g., lifespan, socioeconomic class, cultural beliefs, and ethnicity) require consideration in planning an effective therapeutic approach.<sup>153</sup> The psychosocial-spiritual status and cultural beliefs can be a driving factor in successful outcomes. Engaging the individual in honest discussion, listening to concerns or feelings, and sharing rehabilitation needs to set mutually achievable goals will enhance outcomes.<sup>11,203</sup>

As medical innovations help people with cancer live longer, there has been a shift in the way we approach cancer treatment. Shifting from the search for a cure to managing the disease as a chronic condition necessitates a more comprehensive and integrated management approach.<sup>165</sup> There is greater emphasis on maximizing function and improving QOL with a more holistic approach throughout the various phases of intervention and management.

The therapist will be involved in all phases of care, including prevention, restoration, support, and palliative care. *Prevention* lessens the impact of anticipated disability through education and training. *Restorative care* focuses on restoring physical function as much as possible. *Supportive care* assists in coping with the condition while maintaining maximal functional capacity. *Palliative care* provides comfort during function and ADLs to minimize dependence while offering emotional support.<sup>108</sup>

### **Benign Tumors**

The therapist may be asked by clients to examine unusual skin lesions or aberrant tissue such as unusual moles, ganglion, fibromas, or lipomas. A general screening examination is required with history, age, and risk factors taken into consideration. The ABCD (asymmetry, border, color, diameter) skin cancer screening examination can be employed with documentation of findings for any skin changes.

Benign fatty (lipoma) or fibrous tumors (fibroma) commonly located in the subcutaneous tissues can be located anywhere in the body. Lipomas are found most often in locations where fat accumulates, such as the abdomen, thighs, upper arms, back, and breast. These masses are usually round or oval in shape, soft,

*Continued.*

## **SPECIAL IMPLICATIONS FOR THE THERAPIST 9-1**

### **Oncology/Cancer**

#### **PREFERRED PRACTICE PATTERNS**

See individual cancer as discussed in each chapter. Practice patterns are determined by site-specific clinical manifestations and resulting level of disability and presence of functional limitations. Side effects of treatment and the presence of comorbidities, such as coronary artery disease, diabetes, arthritis or any others, may also determine appropriate practice patterns.

#### **The Role of the Physical Therapist in Cancer Treatment**

Treatment for cancer has improved over the past 20 years, but often results in functional deficits caused by the tissue resection or segmental bone, joint, or limb amputation. Treatment can result in severe disfigurement; cancer is the major cause of amputation in children. Site-specific cancer issues (e.g., cognitive impairment with brain tumors); postsurgical problems (e.g., limited motion, soreness, disuse, pain, fatigue, sensory loss, weakness, deep venous thrombosis and emboli, lymphedema, or sleep disturbance); and side effects of radiotherapy, chemotherapy, and bone marrow or stem cell transplantation often require physical therapy intervention and education.<sup>149,153</sup>

At the present time, standard protocols do not exist for problems associated with cancer and cancer treatment encountered by the physical therapist. Indications and precautions for oncology patients are wide ranging, varied, or nonexistent regarding cardiovascular training, stretching, weight-training, other exercise, or intervention by the physical therapist for any of the problems associated with this condition and its treatment.

There are many individuals with cancer who would benefit from consultation with a physical therapist during the early stages of their cancer treatment. Weakness, inflexibility, osteoporosis, risk of falls, altered or diminished breathing patterns, and lymphedema are just a few of the challenges faced by many of our

**Table 9-8** Side Effects of Cancer Treatment

Surgery	Radiation (See Table 5-7)	Chemotherapy	Biotherapy	Hormonal Therapy	Transplant (Bone Marrow, Stem Cell)
Fatigue	Fatigue	Fatigue	Fever	Hypertension	Severe bone marrow suppression
Disfigurement	Radiation sickness	GI effects	Chills	Steroid-induced diabetes	Mucositis
Loss of function	Immunosuppression	Anorexia	Nausea	Myopathy (steroid-induced)	Nausea and vomiting
Infection	Decreased platelets	Nausea	Vomiting	Weight gain	Graft versus host disease (allogenic graft only)
Increased pain	Decreased white blood cells	Vomiting	Anorexia	Hot flashes	Delayed wound healing
Deformity	Infection	Diarrhea	Fatigue	Impotence	Veno-occlusive disease
Bleeding	Fatigue	Constipation	Fluid retention	Decreased libido	Infertility
Scar tissue	Fibrosis	Anxiety and depression	CNS effects	Vaginal dryness	Cataract formation
Fibrosis	Burns	Fluid/electrolyte imbalance from GI effects	Slowed thinking		Thyroid dysfunction
	Mucositis		Memory problems		Growth hormone deficiency
	Diarrhea	Hepatotoxicity	Inflammatory reactions at injection sites		Osteoporosis
	Edema	Hemorrhage	Anemia		Secondary malignancy
	Hair loss	Bone marrow suppression	Leukopenia		
	Ulceration, delayed wound healing	Anemia	Altered taste sensation		
	CNS/PNS effects	Leukopenia (infection)			
	Malignancy	Neutropenia			
		Thrombocytopenia			
		Decreased bone density with ovarian failure <sup>180a</sup>			
		Muscle weakness			
		Skin rashes			
		Neuropathies			
		Hair loss			
		Sterilization			
		Stomatitis, mucositis (oral, rectal, vaginal)			
		Sexual dysfunction			
		Weight gain or loss			

CNS, Central nervous system; PNS, peripheral nervous system; GI, gastrointestinal.

lumpy, and easily moveable. They may be small (pea-size) or as large as 3 to 4 inches across. Palpation reveals defined borders and a mass that is not fixed but moves readily with pressure along the edge.

These benign tumors are usually painless but can be tender when palpated. Many people who discover the lump are understandably concerned about cancer. Any suspicious integumentary or soft tissue mass must be evaluated medically, especially in the client with any additional risk factors. Only a pathologist can diagnose or rule out these types of lesions.

### Side Effects of Cancer Treatment

Table 9-8 compares the potential side effects associated with the major treatment modalities discussed in this section. See Chapter 5 for discussion of the intended and adverse systemic effects of chemotherapy agents, radiation sickness, radiation recall, CNS effects of immunosuppression, and steroid-induced myopathy.<sup>4</sup>

The ACS provides an on-line guide to drugs used in the treatment of cancer with common side effects listed.<sup>4</sup> The NCCN offers a number of clinical practice guidelines for cancer in general and for specific types of cancer.<sup>133</sup> The ACS offers suggestions for optimizing the preservation of fertility for men and women after cancer therapy.<sup>6</sup>

Each individual will experience and report discomfort in a slightly different way. The occurrence of symptoms is a stressor of its own, sometimes initiating a response of fear behaviors and distress. The idea of symptom distress (SD) as an additional side effect of cancer treatment is a fairly new concept.<sup>106,121</sup> Individual perception of symptoms includes whether the person notices a change in how he or she usually feels or behaves, intensity of the symptoms, and the impact of both the presence and intensity of symptoms on daily activities, function, and QOL. Response to SD includes physiologic, psychologic, sociocultural, and behavioral components. The therapist may have a role in helping people assess their symptoms and amount of distress associated with symptoms, helping them to monitor their own level of health.<sup>105</sup>

The most common and often distressing side effect of cancer and cancer-related treatment is fatigue. The therapist can be very instrumental in offering information and ideas about energy conservation (see Box 9-8). The therapist can help the client set priorities, pace and delegate activities and responsibilities, and provide labor-saving devices and ideas. Scheduling activities at times of peak energy is important along with a structured daily routine that focuses on one activity at a time. The importance of socializing, relaxing, and finding quiet moments of pleasure cannot be

emphasized enough. The therapist may also be involved in relaxation and stress management with referral for nutrition consultation, sleep therapy, and depression when indicated.<sup>133</sup>

Exercise to improve functional capacity, increase activity tolerance, manage stress, and improve mood is an integral part of fatigue management. Exercise has also been examined in a small pilot study of nine individuals with advanced cancer enrolled in a home hospice program.<sup>161</sup> A physical therapist guided participants in the selection of several activities (such as walking, performing arm exercises with resistance, marching in place, and dancing). These were performed at different times throughout the day on a schedule devised jointly by the therapist and participant.

All participants were able to increase their activity level over a 2-week period without increased fatigue. There was also a trend toward increased QOL and decreased anxiety. Although more research is needed, enhanced activity shows promise as a fatigue management strategy even at the end of life.<sup>161</sup>

### Physical Therapist's Evaluation

In a physical therapy practice, anyone with a previous history of cancer, known cancer risk factors, and/or over the age of 40 should be screened for red flags suggestive of cancer. The therapist is a key professional in offering education for risk factor modification and cancer prevention. For the individual with a current diagnosis of cancer, an overall health assessment is important in providing the optimal exercise program. Physical examination will include observation, inspection, auscultation, percussion, palpation, and special tests. Guidelines for physical assessment, review of systems, and visceral palpation by physical therapists are available.<sup>70</sup> Recommended rehabilitation protocols during medical intervention with consideration for the specific cancer treatment are available for physical therapists to consider.<sup>67,219</sup>

The clinical behavior of the majority of musculoskeletal tumors is such that the symptoms are shared with a wide range of nontumorous orthopedic disorders. Pain, swelling, and local heat accompanying musculoskeletal tumors are also common to inflammatory conditions. In addition, the most likely sites of musculoskeletal tumors are regions frequently involved in sports injuries.<sup>110</sup> Occasionally, the client does recall some sort of injury at the site of a previously unsuspected tumor, and this information further confuses the relationship between trauma and malignancy.<sup>117</sup>

Cardiovascular and pulmonary tests and measures, including heart rate; breath sounds and respiratory rate, pattern, and quality; blood pressure; aerobic capacity test (e.g., 6-minute walk test); and pulse oximetry establish a baseline when developing an exercise program. This is especially important with the aging demographics of cancer survivors. The older people are when diagnosed with cancer, the greater the likelihood of other problems being present such as heart disease, hypertension, stroke, diabetes, osteoporosis, and so on.

Observe for and document any cluster of signs and symptoms for accompanying health conditions or comorbidities from cancer or cancer treatment such as hypoxia, decreased peripheral vascular supply, deep vein thrombosis, hypercalcemia, fluid or electrolyte imbalances, anemia, hypertension, integumentary changes, infection, and so on.

Integumentary, neuromuscular, musculoskeletal, and neurologic assessment should include but is not limited to skin characteristics and condition (including lymph node palpation); anthropometrics (e.g., limb length, limb girth, and body composition); functional strength testing; range of motion; flexibility; arousal, attention, and orientation tests; cranial and peripheral nerve integrity; motor function (e.g., dexterity, coordination, voluntary postures, and movement patterns); deep tendon and postural reflexes; and sensory testing (e.g., light touch, sharp/dull, temperature, deep pressure, proprioception, vibration, and stereognosia).<sup>70,154</sup>

The risk of falling is one of the more serious sequelae of both the local effects of cancer and the systemic consequences of cancer treatment. Weakness, pain, fatigue, orthostatic hypotension, peripheral neuropathy, decreased bone density (osteoporosis), and diminished flexibility, in various combinations, may result in falls. Anyone with metastasized cancer to the spine or long bones may fracture these bones in a fall (or fall because of pathologic fractures), which can result in a serious, long-term disability.

Higher incidences of osteoporosis and osteopenia are found in individuals with cancer, especially women taking aromatase inhibitors or with chemotherapy-induced ovarian failure.<sup>188</sup> Men with prostate cancer on androgen deprivation therapy are also more likely to develop osteoporosis. Management of long-term bone health is an important aspect of comprehensive cancer care.<sup>198</sup>

Falls prevention and education are important aspects of the rehabilitation or exercise program. Assessment of the home environment is essential in providing a falls prevention program (see Box 27-19).

In addition, the therapist must evaluate each client individually, possibly selecting an assistive device in appropriate cases. A walker with auto-stop wheels in the front may be a safer choice for some people than a standard walker that must be repeatedly lifted during ambulation. A wheelchair may be necessary for someone who experiences dizziness, weakness, fatigue, or signs of disorientation.

### Precautions

The therapist must practice standard precautions carefully (especially proper handwashing and infection control principles) to help the individual undergoing cancer treatment avoid infection. Closely monitoring blood counts (and other laboratory values) and vital signs and observing for signs of infection, bleeding, or arrhythmias are important. The therapist should contact the physician when the client exhibits fever or cluster of constitutional symptoms, unusual fatigue

*Continued.*

or tiredness, irregular heart beat or palpitations, chest pain, unusual bleeding, or night pain (see complete list in Box 9-7).<sup>163</sup> Radiated tissue must be treated with care to avoid local trauma; extreme temperatures must be avoided, management of lymphedema may be required, and specific guidelines for the use of physical agents must be followed.<sup>153</sup>

Many people undergoing cancer treatment are using complementary and alternative herbs or supplements that can have an adverse effect when combined with radiation or chemotherapy. If the client perceives disapproval, this information may not be relayed to the appropriate health care professional. By being open and nonjudgmental and inviting more discussion about the use of these techniques, the therapist may be able to bring to light potential risks involved. The client should be advised that most herbal or natural supplements and complementary interventions are designed to support, not replace, traditional medical interventions that have been proved effective.

There are many areas of question for therapists treating clients with a current or past history of cancer. Clinical research in this area is sorely needed. In the absence of evidence-based practice, we must fall back on clinical decision-making based on what evidence is available, understanding of the pathophysiology involved, and common sense in pursuing what is considered "best practice." Toward that end, any therapist working with this population group may want to take advantage of the collective ideas and suggestions made available through the American Physical Therapy Association Oncology Section's List Serve, an excellent resource for asking questions of therapists actively engaged in the treatment of cancer patients/clients. The oncology section also publishes an excellent peer-reviewed journal with pertinent and practical articles written by physical therapists in the field.

### Oncologic Emergencies

Oncology patients/clients can present complex challenges for the physical therapist. Treatment regimens and their potential side effects top the list of important considerations during the physical therapist's intervention. Early recognition of potential emergencies, such as superior vena cava syndrome, tumor lysis syndrome, emergent spinal cord compression, severe thrombocytopenia, and other conditions, is extremely important in reducing morbidity and mortality.<sup>196</sup>

Most of these conditions are uncommon or rare, making knowledge of them even more important so the therapist does not miss early clinical manifestations. Each one is typically associated with a particular type of cancer; knowing the patterns of potentially serious problems linked with individual cancers can help the therapist conduct surveillance with appropriate clients. For example, *superior vena cava syndrome* (SVCS) associated with small cell lung cancer and lymphoma is caused by mediastinal metastasis and central lung lesions compressing the superior vena cava. Presentation of SVCS is insidious with dilated neck veins and facial and arm lymphedema. Treatment may be palliative if the malignancy causing the compressive

force is not curable; curative chemotherapy for lymphoma is the exception.<sup>196</sup>

*Tumor lysis syndrome* (TLS) occurs often in high-grade non-Hodgkin's lymphoma but may only become clinically apparent in a small number of affected individuals. TLS occurs in people with myeloproliferative disorders, such as leukemia and lymphoma, when chemotherapy causes lysis of a massive number of cells in a short period of time. Acute renal failure may occur from the deposition of potassium, phosphate, and uric acid from the cell lysis.<sup>196,203</sup> Symptoms of TLS are most common 6 to 72 hours after chemotherapy begins. The therapist may hear reports of and observe muscle weakness and cramping from TLS. In addition, the therapist must monitor for arrhythmias, decreased blood pressure, and tachycardia during activity.

*Spinal cord compression* affects up to 30% of individuals with disseminated cancer from lung, breast, prostate, multiple myeloma, and colon. The thoracic spine is targeted most often, followed by the lumbo-sacral region. Back pain, muscle weakness, gait changes, or other signs and symptoms of cord compression may develop slowly or may progress rapidly; prognosis is better with slow onset.

The therapist should conduct surveillance examinations of serial muscle testing to detect decline in motor function potentially associated with spinal cord compression for individuals undergoing treatment for any of the cancers listed. A stable spine is essential before progressing to out-of-bed activities; surgical stabilization or use of an orthosis may be needed.<sup>196</sup>

Many individuals undergoing treatment for cancer are *thrombocytopenic* (low platelet levels). Severe thrombocytopenia (the definition of "severe" may vary from institution to institution but generally is noted as less than 10,000 cells/mm<sup>3</sup>; some institutions go as low as 5,000) increases the risk of spontaneous bleeding (e.g., intracranial, intramuscular, or joint bleeds). Precautions for thrombocytopenia are discussed further in Chapters 14 and 40. The therapist may be instrumental in preventing intracranial bleeds and falls for anyone with this complication.

### Physical Agents

Various forms of electric, electromagnetic, and other biophysical energy sources have been investigated in light of their potential to relieve some of the symptoms and side effects of cancer, as well as to slow, halt, or destroy tumors. The physical modalities have the capacity to break down cell membrane barriers and stimulate changes in transmembrane potentials, which can trigger growth and development of abnormal tissue.<sup>198</sup>

The use of physical agents in people who have cancer is summarized in Table 9-9. The reader is encouraged to consult the bibliography for references and more specific information about the use of thermal and mechanical agents with this population.<sup>152</sup> Heat modalities should not be used in people undergoing radiation because the thermal effect may enhance the effect of the radiation. Risk for modality use based on stage of medical management is listed in Box 9-5.

**Table 9-9** Common Physiologic Effects and Uses of Physical Agents and Modalities in People with Cancer**Superficial heating agents: hot packs, paraffin baths, infrared lamps, fluidotherapy, local immersion, monochromatic-infrared photo energy (MIRE)\***

Potential Benefits	Contraindications (Do Not Use)	Effectiveness <sup>†</sup>
Increases blood flow to affected area	Over dysvascular tissue (after radiation therapy) and with people who are insensate to temperature or pain in application area	Heat and stretch may decrease pain and muscle spasm in abnormal tissue; modulates pain and facilitates relaxation (gating effect).
Increases metabolism	Over areas of bleeding or hemorrhage (i.e., if there has been long-term corticosteroid therapy or chemotherapy)	Not effective with deep cancer pain or bone pain (NSAIDs used).
Reduces pain, muscle spasm, chronic inflammation	Over an acute injury or inflammation	
Increases relaxation and ROM	Presence of thrombophlebitis	
Provides mild heat ( $\leq 40^\circ \text{ C}$ ) to trunk; vigorous heat ( $\geq 40^\circ \text{ C}$ ) to extremities	Directly over a tumor	
	Over open wounds (except whirlpool at warm temperature)	

**Deep heating agents: diathermy, ultrasound, full-body immersion hydrotherapy**

Potential Benefits	Contraindications (Do Not Use)	Effectiveness <sup>†</sup>
Increases extensibility of collagen tissue, such as scar tissue, tendons (ultrasound)	Over growing epiphyses	Acute stage—there is a cancer treatment used for tumor hyperthermia to kill tumor tissue, administered at greater than therapeutic doses.
Reduces pain and muscle spasm	Over areas of acute hemorrhage (long-term use of corticosteroids or NSAIDs)	Advanced cancer/terminal stage—not indicated over tumor: this will increase tumor growth, often increasing the severity of symptoms such as pain.
Increases ROM	Over acute injury or inflammation	
Alters threshold of nerve conduction	Over insensitive skin; dysvascular or irradiated skin	
Provides mild heat ( $\leq 40^\circ \text{ C}$ ) to trunk; vigorous heat ( $\geq 40^\circ \text{ C}$ ) to extremities	Over tumors (unless trained in hyperthermia)	
Increases metabolism	Over implants or devices, such as pacemakers or defibrillators, insulin pumps, morphine pumps, breast implants, plastic components, joint prosthetics—ultrasound over joint	
	Over reproductive organs; over lumbosacral, pelvic, and lumbar regions if pregnant	

**Cryotherapy: cold packs, ice massage, cold hydrotherapy or baths, vapocoolant spray, cold compression**

Potential Benefits for Acute Musculoskeletal Trauma	Contraindications (Do Not Use)	Effectiveness <sup>†</sup>
Reduces acute inflammation or inhibits edema, muscle spasm, spasticity (transient decrease of spasticity)	Over dysvascular tissue (after radiation therapy) and with people who are insensate to temperature or pain in application area	Acute stage or advanced cancer—tumor treatment: supercooled at below therapeutic temperatures for local, superficial tumor destruction (e.g., liquid nitrogen for precancerous skin lesions).
Alters threshold of nerve conduction	When transient increase of blood pressure might be dangerous (monitor anyone with hypertension)	Immediate postchemotherapy cancer treatment—cold packs to head (cold cap) are suggested to reduce hair loss.
Decreases metabolism	When wound healing is delayed	Chronic stage and cured or in remission—used for usual indications for cold therapy.
Decreases blood flow with later increase in blood flow	If nerve injury has occurred (applies especially to irradiation- or chemotherapy-induced nerve injury)	Occasionally selected by clients for pain relief; must be monitored by health or personal caregiver.
	If Raynaud's disease or peripheral vascular disease is present (exacerbated by chemotherapy)	Treatment of pain in advanced cancer—not as acceptable to some for comfort care.

*Continued.*

**Table 9-9** Common Physiologic Effects and Uses of Physical Agents and Modalities—cont'd**Mechanical agents: traction (sustained or intermittent, mechanical or manual, spinal or peripheral)**

Potential Benefits	Contraindications (Do Not Use)	Effectiveness <sup>†</sup>
Improves motion and mobility in clients with degenerative joint disease, joint hypomobility, or herniated disks	Structural disease (tumor, infection) Acute injury Positive vertebral artery test Positive alar ligament test	Effective when there has not been previous radiation therapy to spine.
<b>External compression: mechanical or manual—Jobst pump, Lymphapress, Wright linear pump, garments, bandages</b>		
Potential Benefits	Contraindications (Do Not Use)	Effectiveness <sup>†</sup>
Reduces edema or lymphedema and pain secondary to edema or lymphedema; improves ROM problems related to edema	Difficulty tolerating treatment (impaired circulation) Phlebitis, DVT, thrombosis in area to be compressed Compression setting should not be greater than 45 mm Hg (see Chapter 13)	Acute stage—may not be indicated. Immediately after cancer treatment, advanced or terminal stage, chronic stage or cured—not indicated for lymphedema management unless cleared of cancer metastasis or recurrence or new cancer in region(s) to be treated.

**Hydrotherapy with agitation (agitation and local immersion hydrotherapy)**

Potential Benefits	Contraindications (Do Not Use)	Effectiveness <sup>†</sup>
Depending on temperature, same as for superficial heat and/or cold in region to be immersed	Depending on water temperature, same as for superficial heat and/or cold in region to be immersed	Same as for superficial heat in region to be immersed.
Wound healing—stimulates circulation to promote healing; removes exudates and necrotic tissue	Agitation should be minimized with painful open lesions, severely traumatized tissue, or recent skin grafts	
Facilitates exercise	Risk of cross infection must be controlled, especially for immunocompromised clients	
Relaxation; pain control		

**Electrical stimulation: neuromuscular electrical nerve stimulation (and FES)**

Potential Benefits	Contraindications (Do Not Use)	Effectiveness <sup>†</sup>
Reduces or eliminates muscle spasm	If there is a potential for pathologic fracture in the area	Wound healing—HVPC or LIDC (microcurrent). Strengthening.
Minimizes disuse atrophy	Any type of implanted device (see above list)	Increased endurance.
Strengthens weak but innervated muscle	Severe cardiopulmonary insufficiency	
Increases circulation secondary to muscle pump	Active phlebitis, DVT, thrombosis in area to be treated	
Functions as a substitute orthotic		

**TENS and electrical stimulation at acupuncture points**

Potential Benefits	Contraindications (Do Not Use)	Effectiveness <sup>†</sup>
Partial or complete alleviation of pain:	Any type of implanted electronic device (pacemaker, insulin pump, morphine pump, defibrillator)	Advantages over narcotic analgesics: few side effects, relatively inexpensive and easy to use. Allows interpersonal interaction and is controlled by the client.
Acute pain		
Postoperative incisional pain	Not useful in control of generalized pain or deep bone pain	During treatment (chemotherapy) is effective as an antiemetic for nausea and vomiting.
Chronic pain	Occasional allergic reactions to gel or adhesive	Immediately after treatment for postoperative pain and chronic pain control for 2-4 months.
Phantom pain		
Peripheral neuropathy pain		
Postherpetic neuralgia		
Advanced malignancy (but not over tumor)	Decreased effectiveness over time	

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ROM, Range of motion; NSAIDs, nonsteroidal antiinflammatory drugs; DVT, deep vein thrombosis; FES, functional electrical stimulation; HVPC, high-voltage pulsed current; LIDC, low-intensity direct current; TENS, transcutaneous electrical nerve stimulation.

\*Under investigation; some reports of adverse response (e.g., burns) when used beyond recommended duration as a result of insensate, avascular conditions.

<sup>†</sup>Safe if cleared for possible cancer recurrence, metastasis, or new cancer in area or areas to be treated and if the sensation and circulation in the area or areas to be treated are not impaired.

**Box 9-5****RISKS FOR MODALITY USE BASED ON STAGE OF MEDICAL MANAGEMENT****Acute Stage**

- Medical diagnosis and treatment for new or newly recurrent cancer
- Potential for disseminated cancer until the medical diagnostic process is completed (except cases of local cancer)
- Stage I cancer: local disease, usually receives a local treatment (e.g., surgery and/or radiation therapy)
- Stage II cancer: option of local treatment (surgery and radiation therapy) without systemic therapy (e.g., chemotherapy); higher risk of metastases or recurrence
- Stage III cancer: systemic therapy, often chemotherapy; the process of micrometastases is unlikely in someone responding to chemotherapy

Risk: high risk; thermal agents should not be used during or in close time proximity to radiation or chemotherapy; general contraindications/precautions apply (e.g., insensate or dysvascular tissue with decreased sensation or decreased blood flow)

**Subacute Stage**

- Immediately after cancer treatment; may extend 6-12 months depending on treatment intervention (e.g., surgery, chemotherapy, radiation); hormone therapy (e.g., tamoxifen or aromatase inhibitors for breast cancer) continues for 5 years
- Acute side effects or toxicities from treatment (e.g., radiation or chemotherapy) begin to subside

Risk: high risk; thermal agents should not be used during or in close time proximity to radiation or chemotherapy; general contraindications/precautions apply (e.g., insensate or dysvascular tissue with decreased sensation or decreased blood flow)

**Chronic Stage**

- Remission or recurrence may occur from 6-12 months up to 5 years or more after cancer treatment
- Chronic states of cancer with risk of death for people living with cancer metastases or advanced disease
- Risk of recurrence decreases over time so that the likelihood of recurrence diminishes the farther the client is from the time of diagnosis and treatment

Risk: Stage I\*—no restrictions on use of physical agents or modalities in the absence of clinical signs or symptoms of potential recurrence or new cancer; client has had recent medical checkup including testing for cancer (e.g., bone scan, serum markers) that is negative; general contraindications/precautions apply (e.g., insensate or dysvascular tissue with decreased sensation or decreased blood flow)

- Stage II\*—moderate-to-low-risk group; same restrictions as stage I
- Stage III\*—moderate risk group; same restrictions as stage I
- Stage IV\* (advanced)—high-risk group; caution should be taken over any painful area or mass; thermal agents should not be used during or in close proximity to radiation or chemotherapy; general contraindications/precautions apply

**Statistically Cured Stage**

- Remission more than 5 years after cancer treatment
- Statistical risk of recurrence is minimal
- Return to lifetime risk of cancer as an individual statistical measure

Risk: low-risk group; no restrictions on use of physical agents or modalities in the absence of clinical signs or symptoms of potential recurrence or new cancer; general contraindications/precautions apply

Courtesy Lucinda Pfalzer, PT, PhD, University of Michigan, 2007. Used with permission.

\*At the time of diagnosis.

The application of therapeutic ultrasound over tumors is contraindicated (especially continuous ultrasound), presumably because it is believed that there is an increased risk of metastasis.<sup>197</sup> Studies conducted on mice have shown that a tumor given large doses of ultrasound will spread because of increasing blood supply to the area.<sup>87,107,184</sup>

The concern that electrical and thermal modalities can increase blood flow and possibly increase micro-metastases in humans has not yet been proved in clinical studies. For a detailed explanation of the possible physiologic effects of therapeutic ultrasound on tumor angiogenesis, see reference 117. For further discussion of the electrical field around cells and how percutaneous application of biophysical modalities can change the electrical potential of tissues for cell division and growth, see reference 38.

As a general guideline, some therapists caution that people with cancer should not be treated with electrical or deep-heating thermal physical agents (ultrasound in particular), even at a site distant from the neoplasm, because the effect of ultrasound on micro-metastases is not known.

Low-level laser treatment has recently been approved by the FDA for the treatment of postmastectomy lymphedema. The laser-beam pulses produce photochemical reactions at the cellular level, thereby influencing the course of metabolic processes, reducing the volume of the affected arm, extracellular fluid, and tissue hardness.<sup>24</sup>

The use of low-level laser over areas where carcinoma was originally found has not been investigated. Manufacturers of laser equipment suggest that a history of carcinoma is a contraindication for the use of Class 3 laser. Information is lacking regarding the use of Class 1 laser. If we consider the method of action of the laser (increased transport across the mitochondrial barrier), prior carcinoma remains a contraindication in the use of laser.<sup>54</sup> Research in this area is needed.

There may come a time in the client's situation (especially in the case of advanced-stage cancer or limited life expectancy) when palliation, especially pain control, is more important than the risks of metastasis with the use of some modalities. However, this must still be determined based on clinical presentation, potential risks, and benefits. For example, if a tumor is impinging or even wrapped around a nerve, ultrasound over the site may increase tumor growth, causing further nerve compression. Short-term pain relief using this modality may result in more pain even in the short term and would not be advised.<sup>44</sup>

*Continued.*

### Sexual Issues

Sexual dysfunction is a frequent side effect of cancer treatment, especially for those adults with cancer of the reproductive organs (e.g., breast, prostate, testicle, ovary, and uterus) and after Hodgkin's disease. The most common problems include loss of desire for sexual activity, erectile dysfunction in men, and dyspareunia in women. Unlike many other physiologic side effects, sexual problems do not tend to resolve within the first year or two of disease-free survival but remain constant.<sup>177</sup>

Physical therapists are often in a unique position to assist people with sexual concerns because of their repeated close contact with the affected individual. Sexual function is an important aspect of QOL and requires a brief assessment. In oncology settings, it is often helpful to designate and train a member of the team as the expert on sexuality issues.<sup>177</sup>

The therapist who is comfortable and knowledgeable in discussing sexual issues may be able to provide more focused assistance to the individual who is trying to adjust to changes in sexual style and practices as a result of the illness. Understanding the range of values and sexual history that clients bring to the clinical situation and respecting appropriate provider-client boundaries are important.<sup>160</sup> More specific information on this topic is readily available.<sup>8,88,146,180</sup>

### Palliative and Hospice Care

When curative measures have been exhausted and a cure is no longer possible or available, symptom management or palliative care may be offered. Palliative care is given to improve the QOL for people who have a serious or life-threatening disease. The goal is to prevent symptoms; side effects caused by treatment of the disease; and psychologic, social, and spiritual problems related to the disease or its treatment. When prevention is not possible, then treatment becomes the intervention.<sup>135,162a</sup>

The CARING criteria is a practical tool to help identify those individuals who may benefit from a palliative approach with end-of-life discussions and aggressive symptom management. The criteria are simple items easily identified upon hospital admission. The criteria include the following<sup>58</sup>:

**C:** Primary diagnosis of Cancer (especially if cancer has metastasized)

**A:** Two or more hospital Admissions for a chronic illness in the last 12 months

**R:** Resident in a nursing home

**I:** ICU admission with multiple organ failure (MOF)

**N:** Noncancer hospice (meeting two or more of the National Hospice and Palliative Care Organization's (NHPCO))

**G:** Guidelines

Scoring for risk of death is as follows:

Low:             $\leq 4$

Medium:      5-12

High:            $\geq 13$

This set of screening criteria is highly predictive of death within 1 year in a hospitalized population. Even if the person ends up with a better result than predicted, there is no harm in instituting palliative care. The client ends up with a completed advance directive and is less likely to experience untreated pain. When death is imminent, hospice, defined as support and care given for people in the last phase of an incurable disease so they may live as fully and comfortably as possible,<sup>135a</sup> may be provided in a free-standing hospice center, hospice hospital unit, long-term care facility, or at home. At the center of hospice and palliative care is the belief that everyone has the right to die pain-free and with dignity and that families should receive the necessary support to allow this to occur.

According to the guidelines of the World Health Organization (WHO),<sup>217</sup> the term *terminally ill patient* refers to individuals with cancer whose life expectancy is less than 90 days, and the index of their physical state (defined by the Karnofsky Index; see Table 30-6) is below 50. Individual hospice agencies may use time periods other than 90 days as their qualification standard.

Although the cost of hospice may be covered by private insurance or by the client/family out-of-pocket, Medicare has three key eligibility criteria as follows:

The patient's doctor and the hospice medical director use their best clinical judgment to certify that the patient is terminally ill with a life expectancy of 6 months or less, if the disease runs its normal course.

The patient signs a statement choosing to receive hospice care rather than curative treatments for his/her illness.

The patient enrolls in a Medicare-approved hospice program.

Palliative care for the terminally ill is aimed at improving the QOL of both the individual and family members. The primary goal is to decrease the physical and psychologic suffering of the individual while providing spiritual and emotional support. Every effort is made to help the individual achieve as full a life as possible, with minimal pain, discomfort, and restriction. Many medications, especially morphine, are used for pain control. Emphasis of hospice care is toward emotional and psychologic support for the client and the family, focusing on death as a natural end to life.<sup>134</sup>

Physical therapy may enhance the QOL of individuals receiving palliative care, as well as dying individuals receiving hospice care. Disability in individuals with advanced cancer often results from bed rest, deconditioning, and neurologic and musculoskeletal complications of cancer or cancer treatment. Weakness, pain, fatigue, and dyspnea are common symptoms.

Physical therapy intervention aims to improve level of function and comfort. Physical function and independence should be maintained as long as possible to improve QOL and reduce the burden of care for the caregivers.<sup>115</sup> Pain management and relief, positioning to prevent pressure ulcers and aid breathing, endur-

ance training and energy conservation, home modification, and family education are just a few of the services the physical therapist can offer hospice clients and families. The therapist is an important team member in helping clients remain functional and retain dignity and control at the end of life.<sup>162a</sup>

At the present time there is very little evidence that rehabilitation interventions can impact function and symptom management in individuals who are terminally ill. Clinical experience suggests that the application of rehabilitation principles is likely to improve their care.<sup>170</sup> Evidence-based research may help expand reimbursement under Medicare to include physical therapy as a core service.<sup>162a</sup> Therapists working with hospice programs are encouraged to attend interdisciplinary team meetings whenever possible—even if reimbursement for the time is not possible or the therapist has not been specifically invited or included. Discussing and demonstrating ways in which the physical therapist can benefit clients, while acknowledging the costs (and cost savings), can help advance the overall work of physical therapists in hospice care.<sup>162a</sup>

For physical therapists interested or involved in hospice care, there is an APTA Oncology Section-sponsored special interest group (SIG) available for support and information: Hospice and Palliative Care SIG ([www.oncologypt.org/sigs/hospice.cfm](http://www.oncologypt.org/sigs/hospice.cfm)). The Hospice and Palliative Care SIG can help therapists who have a common interest in the treatment of life-limiting conditions meet, confer, and promote these interests.

#### Radiation Hazard for the Health Care Worker

Implant radiation therapy requires personal radiation protection for all staff members who come in contact with the client (this topic is discussed in the section on Radiation Hazard for Health Care Professionals in Chapter 5).

## CANCER, PHYSICAL ACTIVITY, AND EXERCISE TRAINING

Investigators have begun extensive research in the area of exercise and cancer. As with the prevention and management of heart disease, obesity, osteoporosis, and diabetes, exercise has an important role in relation to cancer. More and more studies of cancer as a prevention strategy, as a means to ameliorate side effects of cancer treatment, and to promote improved health among cancer survivors are being published. The results of studies are varied and wide-ranging and complicated by the fact that exercise can be aerobic, strength training, flexibility, balance training, and conditioning or any combination of these forms. Each type of exercise has its own physiologic and psychologic benefits in the normal, healthy adult population.

The effects of each type of exercise on individuals with cancer are being investigated in many studies. Additionally, not all cancers are alike or affect the body in the

same way; cancer exercise benefits may vary based on cancer type, stage, type of treatment, changes made by treatment, and so on. Exercise appears to be safe, but long-term outcomes have not been reported. Some types of exercise have been shown detrimental to the immune system and this must be considered (see discussion in Chapter 7).

Only a composite summary is provided here. Therapists working with the oncology population are encouraged to study each individual cancer encountered to find the best choice of prescriptive exercise published in the literature.

#### Exercise as a Cancer Prevention Strategy

Physical activity is defined as body movement caused by skeletal muscle contraction that results in quantifiable energy expenditure. Both epidemiologic and laboratory data indicate that the level of physical activity in which an individual engages may affect cancer risk. Exercise is distinguished from other types of physical activity by the fact that the intensity, duration, and frequency of the activity are specifically designed to improve physical fitness.

Based on available data, a role for exercise in specifically reducing cancer risk has been shown for breast and colorectal cancer, with more equivocal evidence for others such as melanoma, lung, and prostate cancers.<sup>182</sup> The exact amount of exercise needed to prevent cancer is debatable. It is currently not known what would be most beneficial for which cancers, at which stage of disease, or treatment.<sup>183</sup> The ACS advises moderate habitual physical activity as a potentially protective measure against certain types of neoplasms, particularly tumors of the colon and the female reproductive tract. The activity should cause a slight increase in heart rate and breathing lasting 30 minutes, at least 5 days a week.

Exercise-induced changes in the activity of macrophages, natural killer cells, lymphokine-activated killer cells, neutrophils, and regulating cytokines suggests that immunomodulation may contribute to the protective value of exercise (see also the section on Exercise, Physical Activity, and the Immune System in Chapter 7).<sup>122,216</sup>

#### Exercise for the Person with Cancer

Exercise programs also appear to have a beneficial influence on the clinical course of cancer, at least in the early stages of the disease. At the present time, cytokine modulation with exercise is receiving considerable research attention. Researchers theorize that exercise can regulate production of certain hormones, which when unregulated, may spur tumor growth.

With 10 million Americans alive today who have been through the cancer experience, it is important to develop interventions to enhance immune function, prevent or minimize muscle wasting thus counteracting the detrimental physiologic effects of cancer and chemotherapy, and maintain QOL after cancer diagnosis. Physical activity and exercise training are interventions that address a

broad range of QOL issues, including physical (e.g., muscular strength, body composition, nausea, and fatigue), functional (e.g., functional capacity), psychologic (e.g., coping and mood changes), spiritual, emotional, and social well-being.<sup>37</sup>

Studies examining the therapeutic value of exercise for people with various cancers during primary cancer treatment suggest that exercise is safe and feasible, improving physical functioning and some aspects of QOL.<sup>36,101,175</sup>

### **Screening and Assessment**

Medical screening should be conducted with all clients before their participation in an exercise program.<sup>1</sup> This type of screening is especially important for people with cancer who receive various levels of treatment that can affect the physiologic response to exercise. For example, fatigue is a common symptom of nearly every form of cancer treatment.

The therapist will need to take a detailed history of treatment administered to date, examine laboratory results, and distinguish between fatigue from deconditioning and fatigue from medical interventions to determine the most effective and efficient approach to rehabilitation. The medical history should also look for conditions not related to cancer, such as hypertension, diabetes, coronary artery disease, and preexisting orthopedic conditions. The person's current physical condition, condition before disease onset, and age are also important variables.<sup>214</sup>

A self-reporting survey instrument called the Cancer Rehabilitation Evaluation System (CARES; formerly called the Cancer Inventory of Problem Situations [OPS]) is a useful tool for evaluating rehabilitation needs and interventions.<sup>66,173</sup> The therapist must understand the stages of the disease and know the type and timing of the medical intervention, especially for radiation and chemotherapy. The body's physiologic response to these agents (e.g., fatigue, neuropathy, or chemo brain) may alter the normal training response and affect tolerance for exercise and compliance with exercise programs. Cognitive rehabilitation techniques may be needed to improve patient/client compliance, function, and QOL.<sup>63</sup>

Cardiac dysfunction months to years after chemotherapy can result in left ventricular failure, cardiomyopathy, and/or congestive heart failure. These conditions may impact the client's ability to exercise. Signs and symptoms of subclinical cardiac conditions may develop with the initiation of an exercise program. Careful history taking and clinical assessment may result in early detection and intervention, potentially reducing morbidity.

Auscultation to screen for abnormal lung or heart sounds is important to identify any precautions or contraindications to exercise. The individual is not likely to be able to sustain exercise levels if there are any physiologic abnormalities present. Medical consult may be required before initiating a training program.

### **Monitoring Vital Signs**

Monitoring physiologic responses to exercise is important in the immunosuppressed population. Exercise intensity determined by training heart rate may be difficult to use since some people have inappropriate heart

responses to exercise and large physiologic changes on a day-to-day basis from disease and treatment (e.g., changes in medications).

Baseline testing is important to determine safe guidelines and to provide a starting place against which to measure improvement and to identify the individual's functional exercise level. A hypertensive response to exercise is common among individuals with cancer and undergoing cancer treatment. Starting an aerobic training program is not advised if such a response is observed during testing.<sup>163</sup>

Exercise intensity can be guided by heart rate ranges based on oxygen consumption or metabolic equivalent (MET) levels. The therapist can use test results to prescribe a program starting at approximately 60% of the individual's maximum level. The therapist uses prior exercise levels, prior exercise capabilities, baseline function, and individual abilities even when using the predictive formula because each client may respond differently (unpredictably).<sup>163</sup>

The therapist (or client) should always monitor oxygen saturation with pulse oximetry and monitor heart rate (for arrhythmias), pulse rate, breathing frequency, and blood pressure before, during, and after the treatment session. Borg Ratings of Perceived Exertion (RPE) scale (see Table 12-13) or other scales can be used to determine level of symptom distress or severity. RPE is also used when the client is taking cardiac medications that blunt heart rate response to exercise or when other conditions and comorbidities are present that may prevent the use of target heart rate formulas.

Watch closely for early signs (dyspnea, pallor, sweating, and fatigue) of cardiopulmonary complications of cancer treatment. The activity level of someone with anemia also may require adjustment. This client may have elevated pulse and respiratory rates because of hypoxia, with increased cardiac output resulting from the body's effort to maintain an adequate oxygen supply.

### **Exercise During and After Chemotherapy or Radiation Therapy**

Bone marrow suppression is a common and serious side effect of many chemotherapeutic agents and can be a side effect of radiation therapy in some instances such as when radiation dosage exceeded 50 Gy in the past or currently when high levels of radiation are used to prevent death despite potential radiotherapy toxicities later. Therefore it is extremely important to take a client history of current or past radiation therapy dosages and to monitor the hematologic values in clients receiving these treatment modalities.

The therapist must review these values before any type of vigorous exercise or activity is initiated. Current guidelines recommend that individuals undergoing chemotherapy or radiation therapy should not exercise within 2 hours of the treatment because increases in circulation may attenuate (alter or change) the effects of the treatment.<sup>67</sup> Although this recommendation is not based on evidence-based research, it is a guideline followed by the National Institutes of Health (NIH) because of the physiologic effects of moderate to vigorous physical activity and exercise on the redistribution of cardiac output and

**Box 9-6****WINNINGHAM PRECAUTIONS TO AEROBIC EXERCISE IN CHEMOTHERAPY CLIENTS\***

• Platelet count	<50,000/ml
• Hemoglobin	<10 g/dl
• White blood cell count	<3000/ml; >10,000 with fever (no exercise)
• Absolute granulocytes	<500/ml

\*Single threshold values are not usually clinically relevant but provide a general guideline. For example, hemoglobin levels have the most variability from client to client; protocols vary from center to center.

Modified from Winningham ML, MacVicar MG, Burke CA: Exercise for cancer patients; guidelines and precautions, *Phys Sportsmed* 14:125-134, 1986.

blood flow to the working muscle. In the case of both radiation therapy and chemotherapy, there is a potential to enhance treatment toxicity with the shift in blood flow. The suggested 2-hour delay is reasonable given the half-life of most chemotherapeutic agents and the rate of decay of fractionated doses of radiation.<sup>151</sup>

Moderate intensity aerobic exercise (walking for 20 to 45 minutes, 3 to 5 times per week at 50% to 70% of measured maximum heart rates during 7 weeks of radiation) has been shown to maintain erythrocyte levels during radiation treatment (of breast cancer).<sup>49</sup> Physical activity can also improve mood and reduce anxiety and mental stress for people undergoing chemotherapy. Independence and QOL improve as functional ability improves.<sup>44,46,161</sup> A helpful guideline to indicate when aerobic exercise is contraindicated (or when reevaluation of the exercise program is indicated) in chemotherapy clients is given in Box 9-6. Keep in mind these values are primarily educated estimates based on clinical consensus; there is a need for further research and stronger evidence to support these values.<sup>151</sup>

Older adults, especially older adults with bone disease or significant comorbidities and impairments, such as arthritis or peripheral neuropathies, still need help with balance, strength, and coordination to remain safe from falls and injuries.

### Exercise for Cancer-Related Fatigue

Fatigue related to cancer treatment is common and disabling for many people. People in cancer treatment are often advised to rest after chemotherapy, but aerobic exercise and physical activity have been shown to help improve energy level and stamina, reduce fatigue, reduce nausea, increase muscle mass, and increase daily activities without increasing fatigue. The use of exercise as an adjunct intervention for CRF is gaining in favor as an effective strategy.<sup>191</sup> Traditional (e.g., walking or aerobics) and alternative forms of exercise (e.g., Tai chi or yoga) are being investigated.<sup>65,206</sup> Exercise may increase the body's ability to recover from the effects of chemotherapy.<sup>9</sup>

Much of the exercise-related research is focused on breast cancer, but aerobic exercise after bone marrow transplantation<sup>43,172</sup> and exercise during treatment of

cancers, such as multiple myeloma,<sup>33</sup> solid tumors, and lymphoma, have been studied.<sup>206</sup> Exercise combined with improved nutrition for CRF and deconditioning has also been reported successful in demonstrating significant improvements in the 6-minute walk test distance, the squat test, and fatigue level.<sup>142</sup>

Clients receiving chemotherapy and radiation therapy experiencing CRF who are already on an exercise program may need to exercise temporarily at a lower intensity and progress at a slower pace; the goal is to remain as active as possible. For sedentary individuals, low intensity activities, such as stretching and brief, slow walks, can be implemented and slowly advanced.<sup>20</sup>

However, it can be difficult to convince someone who is extremely tired (and especially those who did not exercise before their cancer diagnosis) that exercise will improve his or her symptoms. The therapist may have to begin with discussions over a period of time about the importance of exercise. This is especially important if the person is significantly deconditioned. The therapist can begin with an assessment of previous exercise or activity patterns. Ask the following questions:

- Can you do your normal daily activities?
- Can you participate in a formal or informal exercise program?
- What is your normal amount and frequency of exercise?
- Have you had to modify or change your exercise level or other activity patterns since the development of fatigue?

Symptoms of fatigue, headache, and lethargy begin in most people when hemoglobin falls to 12 g/dl. Mild-to-moderate graded exercise is possible for many people at this level. Symptoms become more pronounced when hemoglobin decreases to 10 g/dl, reducing exercise capacity.

Exercise is not always possible for most people when the hemoglobin level is 8 g/dl or less. Hemoglobin levels should be maintained around 12 g/dl during the administration of chemotherapy,<sup>13</sup> but protocols vary from institution to institution and even from one physician to another within the same facility. Bloodless medicine (see discussion in Chapter 14) has made it possible for clients to tolerate lower hemoglobin levels previously thought unacceptable without compromising oxygen delivery. See also exercise guidelines provided in Tables 40-8 and 40-9, keeping in mind that most oncology settings have their own guidelines that may be more liberal. For example, in some oncology settings, exercise is contraindicated when white blood cell count drops below 500/mm<sup>3</sup> (compared to 5000/mm<sup>3</sup> listed in Table 40-8) and when platelets drop below 5000/mm<sup>3</sup> (compared to 20,000/mm<sup>3</sup> listed in Table 40-9).

The American College of Sports Medicine (ACSM) guidelines for termination of testing or training may also be consulted.<sup>1</sup> People with cancer are advised to contact their physician if any of the abnormal responses listed in Box 9-7 develop.

### Exercise and Bone Metastases

See Special Implications for the Therapist: Metastatic Tumors in Chapter 26.

**Box 9-7****SYMPTOMATIC PRECAUTIONS DURING EXERCISE TESTING OR TRAINING**

Anyone with cancer experiencing any of the following (especially brought on or exacerbated by exercise) should contact his or her physician.

- Fever
- Extreme or unusual tiredness or fatigue
- Unusual muscular weakness
- Irregular heartbeat, chest palpitations, or chest pain
- Sudden onset of dyspnea
- Leg pain or cramps
- Unusual joint pain
- Recent or new onset back, neck, or bone pain
- Unusual bruising, nosebleeds, or bleeding from any other body opening
- Sudden onset of nausea during exercise
- Rapid weight gain or weight loss
- Severe diarrhea or vomiting
- Disorientation, confusion, dizziness, or light-headedness
- Blurred vision or other visual disturbances
- Skin pallor or unusual skin rash
- Night pain

Data from Drouin J, Pfalzer IA: Aerobic exercise guidelines for the person with cancer, *Acute Care Pers* 10:18-24, 2001.

**Prescriptive Exercise**

Types, limitations, and precautions of prescriptive exercise intervention in the treatment of cancer, especially cancer pain, are being studied. The programs studied vary in length from 6 weeks for individuals who were going through radiation therapy to 6 months for those in chemotherapy and the entire duration of bone marrow transplantation. The exercise interventions vary somewhat but most include progressive programs of 15 to 30 minute sessions, 3 to 5 days a week, at an intensity equal to 60% to 80% of maximum heart rate (RPE 11 to 14). A perceived exertion of no greater than 12 may be used as a guide when exercise testing is not possible (see Table 12-13).

The frequency and duration of exercise are determined by the clinical status of the person. If weight training is prescribed, high-repetition, low-weight circuit programs are recommended that do not exceed RPE of 14.<sup>109</sup> Other clinical tools for monitoring and more specific guidelines for exercise are available.<sup>45,48,149</sup>

Individuals who exercised more than 60 minutes per day were more likely to report higher levels of fatigue, suggesting a maximum effective dose for individuals receiving adjuvant chemotherapy (in this case for breast cancer). No serious adverse events were reported in any of the studies, although anyone in the high-risk category with serious comorbidities was excluded, and most exercise programs were flexible and symptom-limited.

The reported outcomes of these and other studies show that exercise has a powerful effect on CRF, with fatigue levels reported as 40% to 50% lower in exercising participants. Exercise reduces fatigue and emotional distress and improves QOL.

**Box 9-8****TIPS FOR ENERGY CONSERVATION**

Energy conservation is an organized procedure for finding ways to reduce the amount of effort and energy needed to accomplish a given task. By reducing the amount of energy needed to accomplish a task, more energy is available. Applying principles of energy conservation requires self-examination and assessment of habits and priorities. Making these types of changes requires patience but can result in continued activity over a longer period of time:

- Schedule the most strenuous activities during periods of highest energy.
- Before starting any activity, analyze the task and answer the following questions:
  - Is the task necessary?
  - Can it be eliminated or combined?
  - Am I doing this out of habit?
  - Can it be simplified by combining or eliminating steps?
  - Can a larger job be divided into smaller tasks?
  - Are there any assistive devices or tools that could make the task easier?
  - Can this be done by someone else?
  - Alternate more strenuous tasks with easier ones.
  - Plan frequent rest periods, sit down, or take naps as needed.
  - Cluster activities so that it is not necessary to make frequent trips or walk long distances at home, school, or work.
  - Avoid or keep to a minimum the climbing of stairs.
  - Keep certain tasks, such as housekeeping, to a minimum.
  - Sit down to perform activities of daily living (e.g., tooth brushing, hair combing) or household tasks, including meal preparation.
  - Avoid sitting on low or soft furniture that requires more energy expenditure to get up again.

Modified from Hamburge RR: Principles of cancer treatment, *Clin Manage* 12:37-41, 1992.

Without exception, all of these studies showed lower levels of fatigue and emotional distress as well as decreased sleep disturbance (if this was studied as an outcome) in people who exercised during treatment compared to controls or to baseline scores in single-group designs. A summary of the studies included is available.<sup>132</sup>

Not all people with cancer are able to participate in aerobic exercise. People who ambulate less than 50% of the time or who are confined to bed and those who fatigue with mild exertion may not be candidates for aerobic exercise.<sup>213</sup> Range of motion and gentle resistive work until tolerance for activity improves are still important. Some people may become easily fatigued with minimal exertion. Energy-conservation techniques and work simplification (Box 9-8) may be necessary for the person with chronic fatigue and for those whose functional status is declining. Therapeutic exercise should be scheduled during periods when the person has the highest level of energy.

Generalized weakness associated with cancer treatment can be more debilitating than the disease itself. Whenever possible, exercise, including strength training and cardiovascular training, is an essential component for many people with cancer. Improving strength and endurance aids in countering the effects of the disease

and the effects of medical interventions. Increased physical activity may increase the homeostatic sleep drive to increase nighttime sleep and may help relieve CRF.<sup>33</sup>

Interval exercise or a bedside exercise program may be preferred at first. Interval exercise may be the only treatment possible in this circumstance. This is performed during frequent but short sessions throughout the day with work-rest intervals beginning at the person's level of tolerance. This may be no more than 1 minute of exercise followed by 1 minute of rest, then 1 minute of exercise, and so on. As the person's endurance level increases, the duration of work may be increased and the interval of rest decreased. See also Special Implications for the Therapist: Anemia in Chapter 14.

### **Exercise and Lymphedema**

In the past, therapists were cautioned to carefully design a program that did not cause or exacerbate cancer-related complications such as edema. It was advised that repetitive or strenuous exercise would increase the production of lymph fluid and lymphedema would be the result because lymph nodes were removed during surgery, damaged by radiation therapy, or invaded by the tumor, leaving scar tissue that prevented normal lymph drainage. In fact, it is now known that exercise activates muscle groups and joints in the affected extremity and does not induce lymphedema.<sup>77,78</sup> Resistance training has not been shown to adversely affect lymphedema.<sup>2</sup>

Combining a specific exercise program for each individual with the use of sufficient compression will facilitate the process of decongestion by using the natural pumping effect of the muscles to increase lymph flow while preventing limb refilling. Most clinicians experienced in lymphedema treatment agree on basic guidelines for exercise. See further discussion in Chapter 13.

### **Exercise and Advanced Cancer**

With improved detection and treatment, more and more people are living with cancer as a controllable chronic disease or in advanced stages of cancer. There is insufficient research on exercise in such individuals to make specific recommendations for physical activity and exercise. In such cases, therapists are advised to prescribe exercise based on individual needs and abilities.

General training precautions for warmup and cool down should be followed while monitoring for abnormal heart rate or blood pressure responses and observing each individual for pathologic symptomatic responses (e.g., hypertension, chest pain, onset of wheezing, claudication or leg cramps, shortness of breath, and dizziness or fainting). Clients should be encouraged to remain adequately hydrated at all times unless medically directed otherwise.

Compromised skeletal integrity, especially in the presence of muscle wasting, increases the risk of fracture and may prevent weight-bearing activities. Aerobic exercise may have to begin with non-weight-bearing exercise, such as cycling, rowing, or swimming (for those who are not immunocompromised or neutropenic), with a gradual return to weight-bearing activities whenever possible to prevent loss of bone density. People with severe muscle weakness may tolerate cycling better than

### **Box 9-9**

#### **SPECIFIC EXERCISE PRECAUTIONS FOR CANCER SURVIVORS**

- Survivors with severe anemia may need to delay exercise; medical evaluation is required.
- Survivors with compromised immune function or who have had bone marrow transplantation should avoid public gyms and other public places until white blood cell counts return to safe levels; this could take up to 1 year or longer.
- Severe fatigue can keep an individual from doing any exercise; daily stretching is advised, and even 5-minute increments of mild activity (e.g., walking, sit-to-be-fit) should be encouraged.
- Avoid exposure of irradiated skin to chlorine (e.g., swimming pools) until medically approved.
- Survivors with indwelling catheters must observe additional precautions: avoid water or other microbial exposures that can lead to infection; avoid resistance training of muscles that can dislodge the catheter.
- Recumbent stationary biking may be a better option than walking on a treadmill for survivors with significant peripheral neuropathies or gait disturbances.

Data from Doyle C: Nutrition and physical activity during and after cancer treatment: an American Cancer Society guide for informed choices, CA Cancer J Clin 56(6):323-353, 2006.

walking.<sup>148</sup> Interval exercise (periods of exercise alternated with periods of rest) may be used with a goal in mind of increasing the exercise time and decreasing the rest.<sup>148</sup>

### **Exercise for Cancer Survivors**

Being sedentary is a risk factor for several of the most common types of cancer (e.g., breast and colon). Survivors tend to decrease levels of physical activity and exercise during and after completion of their treatment, especially if they were sedentary before their cancer diagnosis.<sup>94</sup> Low-intensity exercise can seem like high intensity for these individuals. In addition, some therapies reduce exercise capacity because of cardiopulmonary, neurologic, and musculoskeletal impairments. Until studies verify these findings, it is assumed that the beneficial effects of activity and exercise on cardiovascular health, bone strength, lean body mass, and balance also apply to cancer survivors.

The type, frequency, duration, and intensity of exercise should be individualized based on the survivor's age, previous fitness level, type of cancer and cancer treatment, and the presence of any additional comorbidities. Some specific guidelines are available in Box 9-9.

Until results of systematic studies are available, the ACS recommends at least 30 to 60 minutes of moderate to vigorous physical activity at least 5 days per week to reduce the risk of cancer, cardiovascular disease, and diabetes.<sup>103,111</sup> There is no reason to think these recommendations would not benefit cancer survivors. Any step toward this goal should be encouraged.

Survivors should be educated to understand that any exercise has a linear benefit with increasing health benefit

with higher volume of physical activity. Caution should be provided that extremely high levels of exercise might increase the risk for infections and exercise-related injuries.<sup>137</sup> See further discussion in the section on Exercise and the Immune System in Chapter 7.

## CHILDHOOD CANCER

### Incidence and Overview

Each year approximately 8400 children in the United States are diagnosed with cancer; approximately 2000 deaths of children 19 and under are attributed to cancer.<sup>96</sup> With recent advances in treatment, 79% of these children will survive 5 years or more (improved from 58% for children diagnosed 30 years ago and an increase of almost 40% since the early 1960s). Cancer is the second leading cause of death among children between 1 and 14 years of age.<sup>96,116</sup> Treatment-related deaths have declined as a result of advances in clinical supportive care (e.g., antibiotic therapy, indwelling venous-access lines, blood products, and enteral and parenteral nutrition) that maximize the benefits and minimize the side effects of cancer therapy.

The types of cancers that occur in children vary greatly from those seen in adults. Leukemias, particularly acute lymphocytic leukemia (ALL); lymphomas (almost half of all childhood cancers involve the blood or blood-forming organs); brain tumors; embryonal tumors; and soft tissue sarcomas are the most common pediatric malignancies, whereas adenocarcinomas (e.g., lung, breast, or colorectal) are more common in adults.<sup>104,116</sup>

Other differences that must be taken into account when treating the child with cancer include the stage of growth and development, stage of psychosocial and cognitive development, and emotional response of the child to the illness and its treatment. The immaturity of the child's organ systems often has important treatment implications.

### Types of Childhood Cancers

The most common pediatric malignancies are ALL, non-Hodgkin's lymphoma, Hodgkin's disease, and primary CNS tumors. Neuroblastoma, Wilms' (kidney) tumor, rhabdomyosarcoma, and retinoblastomas are the types of solid tumors occurring most frequently in children.<sup>116</sup>

*ALL*, the most common childhood malignancy, accounts for almost one-third of all pediatric cancers. White males are affected most often, and although the exact cause is unknown, radiation, chromosomal abnormalities, viruses, and congenital immunodeficiencies have all been associated with an increased incidence of leukemia. See also the section on The Leukemias in Chapter 14.

*Wilms' tumor*, a malignancy that may affect one or both kidneys, occurs in children under the age of 14 years and is slightly more prevalent in females than males. Epidemiologic research suggests an increased incidence in children of men exposed to lead or hydrocarbons. Recently, an association between Wilms' tumor and chromosomal

abnormalities has been established, specifically deletion of a suppressor gene located on the short arm of chromosome 11. This chromosomal anomaly is an autosomal dominant trait requiring evaluation of other family members.

*Neuroblastoma* is the most common extracranial solid tumor in children and the most commonly diagnosed neoplasm during the first year of life. Approximately 500 new cases are diagnosed annually in the United States, and the incidence is higher among whites than non-whites. Neuroblastoma can originate anywhere along the sympathetic nervous system, but more than half the tumors occur in the retroperitoneal area and present as an abdominal mass. Other common sites include the posterior mediastinum, pelvis, and neck. If the bone marrow is involved, bone pain may occur. See the section on Neuroblastoma in Chapter 30.

*Rhabdomyosarcoma* is the most common soft tissue sarcoma and the seventh leading cause of cancer in children. This tumor, which is more prevalent in males than females, originates from the same embryonic cells that give rise to striated muscle. The peak incidence is between the age of 2 and 5 years and a second peak occurs between 15 and 19 years, with much improved survival rates with early detection and treatment today. The most common tumor sites include the head and neck, genitourinary tract, and extremities. Rhabdomyosarcoma of the head and neck can lead to CNS involvement, including cranial nerve palsies, meningeal symptoms, and respiratory paralysis. See further discussion in Chapter 26.

Other common cancers seen in children are bone cancers, both osteogenic and Ewing's sarcomas (see Chapter 26), and brain tumors (see Chapter 30).

### Late Effects and Prognosis

As advances in cancer therapy improve, the prognosis of children with malignancies continues to improve. Over the past 25 years, there have been significant improvements in the 5-year survival rate for many childhood cancers, especially ALL and acute myeloid leukemia, non-Hodgkin's lymphoma, and Wilms' tumor. Between 1974 and 1996, 5-year survival rates among children for all cancer sites combined improved from 56% to 75%.<sup>96</sup> With increasing survival rates, there is a growing concern about the late effects of disease and treatment.

The term *late effects* refers to the damaging effects of surgery, radiation, and chemotherapy on nonmalignant tissues, as well as to the social, emotional, and economic consequences of survival. These effects can appear months to years after treatment and can range in severity from subclinical to clinical to life-threatening. Fortunately, not all children experience such effects, but those who do often end up in the rehabilitation setting.

Late effects have been identified in almost every organ system. Treatment involving the CNS can cause deficits in intelligence, hearing, and vision. Treatment involving the CNS, head and neck, or gonads can cause endocrine abnormalities such as short stature, hypothyroidism, or delayed secondary sexual development. Children treated with anthracyclines (e.g., doxorubicin [Adriamycin]) are

at risk for development of cardiomyopathies, especially with increasing cumulative doses.<sup>189</sup>

Surgery and radiation involving the musculoskeletal system have been associated with defects such as kyphosis, scoliosis, and spinal shortening. Finally, the child who has received radiation or chemotherapy has a tenfold greater chance of developing a second malignancy than a child who has never had cancer.

## References

To enhance this text and add value for the reader, all references are included on the companion Evolve site that accompanies this textbook. The reader can view the reference source and access it on-line whenever possible. There are a total of 220 cited references and other general references for this chapter.

# CHAPTER 10

## The Integumentary System

HARRIETT B. LOEHNE • CATHERINE C. GOODMAN

Skin is the largest body organ, constituting 15% to 20% of the body weight and consisting of three primary layers (Fig. 10-1). The dermis is more distinctly divided into two separate layers referred to as the *papillary dermis* and *reticular dermis*. The structures included in each layer are listed in Table 10-1.

The skin differs anatomically and physiologically in different areas of the body, but the overall primary function of the skin is to protect underlying structures from external injury and harmful substances. The skin is primarily an insulator, not an organ of exchange.

It has many other different functions, including holding the organs together, sensory perception, contributing to fluid balance, controlling temperature, absorbing ultraviolet (UV) radiation, metabolizing vitamin D, and synthesizing epidermal lipids.

### SKIN LESIONS

Approximately one in every four people who consult a physician has a skin disorder. Skin lesions can occur as a result of a wide variety of etiologic factors (Box 10-1). Lesions of the skin or skin manifestations of systemic disorders can be classified as *primary* or *secondary* lesions.

The primary lesion is the first lesion to appear on the skin and has a visually recognizable structure (e.g., macule, papule, plaque, nodule, tumor, wheal, vesicle, pustule). When changes occur in the primary lesion, it becomes a secondary lesion (e.g., scale, crust, thickening, erosion, ulcer, scar, excoriation, fissure, atrophy). These changes may result from many factors, including scratching, rubbing, medication, natural disease progression, or processes of healing.

Birthmarks, commonly caused by a nevus (pl. *nevi*), may involve an overgrowth of one or more of any of the normal components of skin, such as pigment cells, blood vessels, and lymph vessels. Birthmarks may be classified as pigment cell (e.g., mongolian spot, *cafe au lait* spot), vascular (e.g., port-wine stain, strawberry hemangioma), epidermal (e.g., epidermal nevus, *nevus sebaceus*), or connective tissue (e.g., juvenile elastoma, collagenoma) birthmarks.

Most birthmarks do not require treatment. Vascular birthmarks may be removed with laser therapy for cos-

metic reasons. The presence of six or more *cafe au lait* spots over 5 cm in length requires medical investigation, because these may be diagnostic of neurofibromatosis or Albright's syndrome. Mongolian spots (blue-black macules) are found over the lumbosacral area in 90% of Native American, African American, and Asian infants and can easily be mistaken for a large bruise by uninformed individuals (Fig. 10-2).

### SIGNS AND SYMPTOMS OF SKIN DISEASE

*Pruritus* (itching) is one of the most common manifestations of dermatologic disease and a symptom of underlying systemic disease in up to 50% of people with generalized itching, especially among the chronically ill and older populations.<sup>133</sup> It can lead to damage if scratching injures the skin's protective barrier, possibly resulting in increased inflammation, infection, and scarring. Many systemic disorders may cause pruritus, most commonly diabetes mellitus, drug hypersensitivity, and hyperthyroidism (Box 10-2).

*Urticaria*, more commonly known as hives, is a vascular reaction of the skin marked by the appearance of smooth, slightly elevated patches (wheals). These are redder or paler than the surrounding skin and are often accompanied by severe itching. These eruptions are usually an allergic response to drugs or infection and rarely last longer than 2 days but may exist in a chronic form, lasting more than 3 weeks and, rarely, months to years. There is approximately a 50% reduction in numbers of mast cells responsible for urticaria in intrinsically aged skin. This explains the relative rarity of urticaria in the older adult population.

*Rash* is a generalized term for an eruption on the skin, most often on the face, trunk, axilla, and groin, and is often accompanied by itching. As such, a rash can present as a continuum anywhere from erythema, to macular lesions, to a raised papular appearance. Rashes typically occur as a secondary response to some primary agent, such as exposure to the sun, allergens, irritants, or medications or in association with systemic disease.

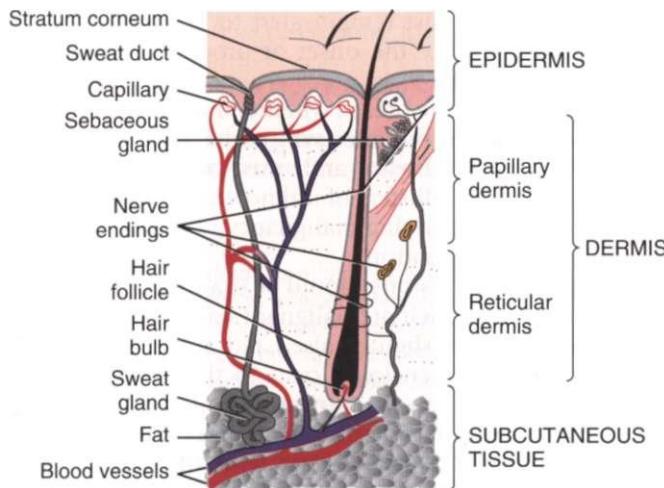
The most common rashes are diaper rash, drug rash, heat rash, and butterfly rash (a cutaneous reaction across the nose and adjacent areas of the cheeks in the pattern

**Table 10-1** Skin Structures

<b>Layer</b>	<b>Structure*</b>	<b>Function</b>
Epidermis	Stratum corneum	Protection (from trauma, microbes); barrier (prevents fluid, electrolyte, and chemical loss)
	Keratinocytes (squamous cells)	Synthesis of keratin (skin protein)
	Melanocytes	Melanosome production; synthesis of melanin, a pigment to protect against sunburn, ultraviolet carcinogenesis; determines skin color
Dermis	Langerhans cells	Antigen presentation; immune response
	Basal cells	Epidermal reproduction
	Collagen, reticulum, elastin	Skin proteins; skin texture
	Fibroblasts	Collagen synthesis for skin strength and wound healing
	Macrophages	Phagocytosis of foreign substances; initiate inflammation and repair
	Mast cells	Provide histamine for vasodilation and chemotactic factors for inflammatory responses
Epidermal appendages	Lymphatic glands	Removal of microbes and excess interstitial fluids; provide lymphatic drainage
	Blood vessels	Provide metabolic skin requirements; thermoregulation
	Nerve fibers	Perception of heat and cold, pain, itching
	Eccrine unit	Thermoregulation by perspiration
Subcutaneous tissue	Apocrine unit	Production of apocrine sweat; no known significance
	Hair follicles	Production; cavity enclosing hair
	Nails	Protection; mechanical assistance
Subcutaneous tissue	Sebaceous glands	Produce sebum (oil to lubricate skin)
	Adipose tissue (fat)	Energy storage and balance; trauma absorption

Modified from Nicol NH: Structure and function: assessment of clients with integumentary disorders. In Black JM, Matassarin-Jacobs E, eds: *Medical-surgical nursing*, ed 5, Philadelphia, 1997, Saunders, p 2176.

\*Understanding the structure of the integument is important in wound management. Knowing why a wound closes the way it does is an essential assessment tool.

**Figure 10-1**

Overall skin structure.

of a butterfly, most often encountered in systemic lupus erythematosus; see Fig. 10-22). Rash appearing on the breast, especially a rash on the areola or nipple with or without accompanying symptoms of itching, soreness, or burning, may be a sign of Paget's disease of the nipple, a rare form of breast cancer.

*Blisters* (vesicle or bulla) are fluid-containing elevated lesions of the skin with clear watery or bloody contents. They can occur as a manifestation of a wide variety of diseases. Blisters may be primarily associated with diseases of a genetic or autoimmune origin or may be secondary to viral or bacterial infections of the skin (e.g.,

#### Box 10-1 CAUSES OF SKIN LESIONS

- Contact with injurious agents (e.g., chemical toxins)
- Contact with infective organisms
- Reaction to medication
- Physical trauma
- Hereditary factors
- Reaction to allergens
- Reaction to radiotherapy
- Systemic origin (e.g., diseases with a cutaneous manifestation; arterial insufficiency)
- Burns (thermal, electrical, chemical, inhalation)
- Neoplasm (paraneoplastic syndrome)

herpes simplex, impetigo), local injury to the skin (e.g., burns, ischemia, pressure, dermatitis), or drug-induced (e.g., penicillamine, captopril).<sup>29</sup> Blisters associated with underlying neoplasm, called *paraneoplastic pemphigus*, may be the first sign of underlying malignancy.

*Xeroderma* is a mild form of ichthyosis or excessive dryness of the skin characterized by dry, rough, discolored skin with the formation of scaly desquamation (shedding of the epithelium in small sheets). This problem is accentuated by the use of drying skin cleansers, soaps, disinfectants, and solvents, and by dry climates.

Other symptoms, such as unusual spots, moles, cysts, fibromas, nodules, swelling, or changes in nail beds, may be observed frequently, since more than half of all people have some basic skin problem at some point in their lives (Box 10-3). Any unusual spot that has appeared recently



**Figure 10-2**

Mongolian spots (congenital dermal melanocytosis). Mongolian spots are common among people of Asian, East Indian, Native American Alaskan American, African, and Latino or Hispanic heritage. They are also present in about 1 in 10 fair-skinned infants. Bluish grey to deep brown to black skin markings, they often appear on the base of the spine, on the buttocks and back, and even sometimes on the shoulders, ankles, or wrists. Mongolian spots may cover a large area of the back. When the melanocytes are close to the surface, they look deep brown. The deeper they are in the skin, the more bluish they look, often mistaken for signs of child abuse. These spots "fade" with age as the child grows and usually disappear by age 5. (Courtesy Dr. Dubin Pavel 2004.)

### Box 10-2

#### SYSTEMIC CAUSES OF PRURITUS

- Candidiasis (systemic, intestinal)
- Diabetes mellitus
- Drug hypersensitivity
- Hyperthyroidism
- Intestinal parasites
- Iron deficiency anemia
- Kidney disease
- Leukemia
- Liver disease
- Lymphomas
- Polycythemia rubra vera
- Renal disease
- Solid tumor malignancies

### Box 10-3

#### SIGNS AND SYMPTOMS OF SKIN DISORDERS

- Pruritus
- Urticaria
- Rash
- Blisters
- Xeroderma (dry skin)
- Unusual spots, moles, nodules, cysts
- Edema or swelling
- Changes in appearance of nails
- Changes in skin pigmentation, turgor, texture

or changed since its initial appearance should be documented and brought to the physician's attention. On the legs, varicosities and stasis changes from poor venous return may be signaled by changes in skin pigmentation, skin turgor (see Fig. 5-7), and skin texture. Edema of the lower extremities can be a sign of multiple systemic illnesses, such as heart, kidney, or liver disease.

### SPECIAL IMPLICATIONS FOR THE THERAPIST

10-1

#### Skin Lesions

##### PREFERRED PRACTICE PATTERNS

**4D:** Impaired Joint Mobility, Motor Function, Muscle Performance, and Range of Motion Associated with Connective Tissue Dysfunction

**7A:** Primary Prevention/Risk Reduction for Integumentary Disorders

**7B:** Impaired Integumentary Integrity Associated with Superficial Skin Involvement

**7C:** Impaired Integumentary Integrity Associated with Partial-Thickness Skin Involvement and Scar Formation

**7D:** Impaired Integumentary Integrity Associated with Full-Thickness Skin Involvement and Scar Formation

Any time a client reports signs or symptoms of skin lesions, further evaluation is necessary, and documentation and possible medical referral may be required. The therapist must remain alert to any skin changes that may indicate the onset or progression of a systemic condition.

Any rash on the breast, whether or not symptomatic or accompanied by other symptoms, raises the suspicion of Paget's disease and must be examined by a medical doctor. Blisters of unknown cause may be the first sign of underlying malignancy requiring immediate medical evaluation.

Certain skin lesions should be examined by a physician because of their premalignant status—for example, actinic keratosis, slightly raised, red, scaly papules; and sebaceous cysts, enclosed cysts in the dermis. Seborrheic keratosis can be moved with friction and may bleed, causing alarm, but this is not a malignancy; the therapist must avoid contact with the skin in that area.

In the case of pruritus, regardless of the cause, the therapist can offer some practical suggestions to help soothe skin, ease the itching, and prevent skin damage (Box 10-4). Bullous skin lesions, including blisters, are associated with risk of exposure to human immunodeficiency virus (HIV) at least comparable to that from blood. Standard Precautions while treating anyone with skin lesions or burns are required.<sup>35</sup>

When examining and documenting the presence of a skin disorder, note the location, size, and any irregularities in skin color, temperature, moisture, ulceration, texture, thickness, mobility, edema, turgor, odor, and tenderness (Box 10-5). If more than one lesion is present, note the pattern of distribution: localized or isolated; regional; general; or universal (total), involving the entire skin, hair, and nails.

**Box 10-4****SKIN CARE STRATEGIES****Reduce Pruritus**

- Avoid scratching.
- Keep fingernails trimmed short to prevent damage in case of unconscious or nighttime scratching.
- Bathe with nondrying, nonfragranced, or unscented soap or other agent when indicated.
- Use soothing bath products, such as Aveeno oatmeal, mineral oil, cottonseed oil, or cornstarch (make a paste with 2 cups cornstarch and 4 cups warm water) added to warm, not hot, bathwater.
- Scleroderma: Apply cooling agents, such as menthol or camphor (e.g., contained in Sarna lotion), to the affected areas.
- Psoriasis: Try skin preparations such as creams containing capsaicin,<sup>82,124</sup> chaparral, or aloe (some advocate the use of pure aloe). Do not apply hot-pepper creams on broken skin.
- Discuss with your physician the possible use of an  $\alpha$ -hydroxy acid (AHA) product or other prescription cream containing urea to dissolve the outer layer of skin and get rid of the dead scales.
- Second-rinse all clothing and bedding to remove residual laundry soap; avoid the use of fabric softeners.
- Wear open-weave, loose-fitting, cotton blend fabrics to allow air to circulate and minimize perspiration, thereby reducing the risk of pruritus; avoid rough, wool, or tightly woven fabrics.
- Avoid temperature extremes that can trigger itching secondary to vasodilation and increased cutaneous blood flow. Avoid hot water (baths or hot tubs) for this same reason.
- Take antihistamines to reduce itching according to physician recommendation.
- Take a shower or bath immediately after swimming; wash with mild soap to remove any residual chlorine or chemicals from the skin.

**Reduce Inflammation**

- Apply topical steroids (available as lotion, solution, gel, cream, or ointment) to affected areas twice daily or as directed. Topical steroids are used to reduce skin inflammation, relieve itching, and control flare-ups of dermatitis and psoriasis. The proper preparation depends on the location and severity of the lesions, and the steroid should not be applied to normal skin.
- Apply tar preparations (available as lotion, solution, gel, cream, ointment, or shampoo) to affected skin as directed. (Some tar preparations can be added to bathwater). The antiinflammatory properties of tars are not so fast acting as

those of topical steroids, but the effect is longer lasting with fewer side effects.

- Tar preparations should not be used on acutely inflamed skin because this may cause burning or irritation.

**Maintain Skin Hydration**

- Bathing has been discouraged because of its alleged drying effect, but some skin care professionals advocate the use of long soaks in a warm (not hot) bath for 15 to 20 minutes, suggesting that soaking for 15 to 20 minutes allows the stratum corneum to become saturated with water.
- Others recommend only showers or brief baths. Both groups agree that drying of the skin is the result of failure to immediately apply the appropriate occlusive moisture, thereby allowing evaporation to occur. Avoid vigorous or brisk towel drying, since this removes more water from the skin and increases vasodilation; gently and quickly pat dry. Immediately (within 2 to 4 minutes of leaving the bath) apply an appropriate emollient or prescribed topical agent.

**Avoid Sun (Light) Exposure**

- Wear sun-protective clothing with tightly woven material covering as much of the body as possible (e.g., long sleeves, long pants, neckline with a collar, hat with broad brim, ultraviolet A/ultraviolet B-protective sunglasses).
- Avoiding sitting near a window at work or for prolonged periods of time.
- Avoid outdoor activities during peak sunlight hours (10:00 AM to 4:00 PM in most time zones but may vary geographically). Limit sun exposure during nonpeak hours.
- Avoid fluorescent lighting or reflected sunlight.
- Wear sunscreen daily and year round, even if driving inside an automobile and on cloudy days.
- Apply sunscreen 30 to 60 minutes before sun exposure to assure maximum absorption. Sunscreen preparations must provide a minimum ultraviolet B sun-protective factor (SPF) of 30 plus an ultraviolet A sunscreen for anyone with a current skin condition or who is at risk for skin cancer. A sunscreen of SPF 15 is considered adequate for anyone else who does not meet this criterion.
- Reapply every 2 hours if you are in the water or perspiring. Sunscreens are not recommended for infants under 6 months of age.
- Do not increase sun exposure because you are wearing a sunscreen. Use of a high-SPF preparation has been shown to lead people to increase time spent in the sun by 25%. Sunscreen is most effective in preventing squamous cell carcinoma.<sup>54</sup>

Note whether the lesions are unilateral or bilateral, note whether they are symmetric or asymmetric, and note the arrangement of the lesions (clustered or linear configuration), especially if these occur as a result of contact with clothing, jewelry, or another external object.

Blisters may be associated with a variety of skin conditions, such as frostbite, dermatitis, burns, pressure, or malignancy, or may possibly occur as a side effect of medications. All blisters should be opened and debrided, except hemorrhagic frostbite blisters and stable, noninfected arterial and heel blisters, which

subsequently should be monitored carefully for signs of infection or deep injury.

Although an intact blister is theoretically sterile, few blisters are substantial enough to remain intact for long. Blister fluid will "set" into a gelatinous film if debridement is delayed. In a burn, this film is the beginning of eschar and is an ideal culture medium for bacteria.

Blister fluid impairs normal function of neutrophils and lymphocytes, which reduces the effectiveness of local immunity. Blister fluid also contains arachidonic

*Continued.*

acid metabolites that increase the inflammatory response and retard the fibrolytic process. All these effects delay healing of the wound.<sup>125</sup>

Special care must always be taken when working with the older adult. Avoiding shear and friction forces during treatment and particularly during repositioning is essential. Extreme caution is also necessary whenever using electrical or thermal modalities (heat or cold) with older people.

Decreased circulation, reduced subcutaneous adipose tissue, and altered metabolism create a situation where initial skin resistance to electricity or poor dissipation of heat or cold can lead to tissue damage. Extra toweling and close supervision are necessary to prevent complications. Utilize appropriate dressings and skin moisturizers for treatment intervention, and avoid using adhesives.

### Laboratory Values

Many factors affect the progression of a skin lesion to wound status and subsequent ability to heal, including use of tobacco, psychosocial status (e.g., comatose, homeless), and nutritional status. Laboratory values, such as prealbumin levels to indicate nutritional status and glucose levels, hemoglobin, and hematocrit to monitor wound healing, provide the therapist with necessary information when setting up and carrying out an appropriate intervention plan.

## AGING AND THE INTEGUMENTARY SYSTEM

The skin undergoes numerous changes that can be seen and felt throughout the lifespan. The most obvious changes occur first during puberty and again during older adulthood. Hormone changes during puberty stimulate the maturation of hair follicles, sebaceous glands, and apocrine and eccrine units in certain body areas. Mild acne, perspiration and body odor, freckles (promoted by sun exposure), and pigmented nevi (moles) are common occurrences.

During adolescence and adulthood, the use of birth control pills or pregnancy may result in temporary changes in hair growth patterns or hyperpigmentation of the cheeks and forehead known as *melasma* or *pregnancy mask*. Other hormonal abnormalities may result in excessive facial and body hair in women (androgen-related). Hormonal and genetic changes also produce male-pattern baldness (alopecia). Smoking is an independent causative factor of facial wrinkles.<sup>43</sup>

The skin exhibits changes that denote the onset of senescence (the process or condition of growing old). These changes may be due to the aging process itself (intrinsic aging), to the cumulative effects of exposure to sunlight (photoaging), or to environmental factors (extrinsic aging). As aging occurs, both structural and functional changes occur in the skin (Table 10-2), resulting clinically in diminished pain perception, increased

### Box 10-5

#### DOCUMENTATION OF SKIN LESIONS

##### Characteristics

- Size (measure all dimensions)
- Shape or configuration
- Color
- Temperature
- Tenderness, pain, or pruritus
- Texture
- Mobility; skin turgor (see Fig. 5-7)
- Elevation or depression
- Pedunculation (stemlike connections)

##### Exudates

- Color
- Odor
- Amount
- Consistency

##### Pattern of Arrangement

- Annular (rings)
- Grouped
- Linear
- Arciform (bow shaped)
- Diffuse

##### Location and Distribution

- Generalized, localized, or universal
- Region of the body; unilateral or bilateral; symmetric or asymmetric
- Patterns (dermatomal, flexor or extensor, random, related to clothing lines)
- Discrete or confluent (running together)

Modified from Hill MJ: *Skin disorders*, St Louis, 1994, Mosby, p 18.

vulnerability to injury, decreased vascularity, and a weakened inflammatory response.

Visible indications of skin changes associated with aging include grey hair, balding and loss of secondary sexual hair, and increased facial hair. For women, excessive facial hair may occur along the upper lip and around the chin. Women may also experience balding after menopause. Men frequently develop increased facial hair in the nares, eyebrows, and helix of the ear.

Other common age-related integumentary changes include lax skin, vascular changes (e.g., decreased elasticity of blood vessel walls; angiomas) (Fig. 10-3), dermal or epidermal degenerative changes, and wrinkling. Wrinkling signifies loss of elastin fibers, weakened collagen, and decreased subcutaneous fat and is accelerated by smoking and excessive sun exposure.

Blood vessels within the reticular dermis are reduced in number, and the walls are thinned. This compromises blood flow and appears physiologically as pale skin and an impaired capacity to thermoregulate, a possible contributing factor to the increased susceptibility of older individuals to hypothermia and hyperthermia. Many other benign changes may occur, including seborrheic keratoses (raised brown or black wartlike growths), lentigines (liver spots, unrelated to the liver but rather sec-



**Figure 10-3**

Spider angioma (arterial spider, spider telangiectasia, vascular spider) is so called because it consists of a central arteriole, radiating from which are numerous small vessels resembling a spider's legs (ranging from pinhead size to 0.5 cm in diameter). Common sites are the necklace area, face, forearms, and dorsum of the hand; may be associated with rosacea, basal cell carcinoma, scleroderma, pregnancy, liver disease, or estrogen therapy or may occur by itself. [From Habif T: *Clinical dermatology*, ed 4, St Louis, 2004, Elsevier, Figs. 23-20, 23-21, p 830.]

secondary to sun exposure), and skin tags (small flesh-colored papules).

A primary factor in the loss of protective functions of the skin is the diminished barrier function of the stratum corneum (outermost layer of the epidermis; see Fig. 10-1). As this layer becomes thinner, the skin becomes translucent and paper-thin, reacting more readily to minor changes in humidity, temperature, and other irritants. There are fewer melanocytes, with decreased protection against UV radiation.

A significant decrease in the number of Langerhans cells occurs, so that by the time a person reaches 70 years of age there is only half the number of Langerhans cells

compared to the number in early adulthood. A reduction in Langerhans cell number represents a loss of immune surveillance and an increased risk of skin cancer.<sup>55</sup>

The epidermis is also one of the body's principal suppliers of vitamin D, which is produced when a hormone, 7-dehydrocholesterol, is exposed to sunlight. At 65 years of age, the levels of that hormone are only about 25% of what they were in youth, contributing to vitamin D deficiency and, because vitamin D plays a vital role in building bone, to osteoporosis as well.

It is generally agreed that one of the major and important contributions to skin aging, skin disorders, and skin diseases is the oxidative damage that occurs to the skin as a result of environmental exposures and endogenous (within the skin itself) factors.

The skin is rich in lipids, proteins, and deoxyribonucleic acid (DNA), all of which are extremely sensitive to the oxidation process. Scientists are striving to understand the mechanisms involved in skin oxidation and the skin defense systems in order to understand skin aging and the mechanisms involved in various pathologic processes of the skin.<sup>57</sup>

## SPECIAL IMPLICATIONS FOR THE THERAPIST 10-2

### *Aging and the Integumentary System*

#### PREFERRED PRACTICE PATTERNS

**4D:** Impaired Joint Mobility, Motor Function, Muscle Performance, and Range of Motion Associated with Connective Tissue Dysfunction

**7A:** Primary Prevention/Risk Reduction for Integumentary Disorders

**7B:** Impaired Integumentary Integrity Associated with Superficial Skin Involvement

The therapist must remain alert to all skin changes, because age-associated blunting of vascular and immune responses may make skin findings more subtle in older adults compared to younger clients with similar disorders. Vascular changes affecting thermoregulation and wound healing require careful consideration when planning therapy intervention.

Likewise, loss of collagen increases susceptibility to shearing force trauma, increasing the risk for pressure ulcers. Wound healing is impaired in intrinsically aged as compared to young skin in that the rate of healing is appreciably slower, but paradoxically the resultant scar is usually more cosmetically acceptable.<sup>55</sup>

Skin diseases and symptoms caused by skin disorders are exceedingly common among the older population. Although these disorders are not usually life threatening they provoke anxiety and psychologic distress. Often, the client has not brought these concerns to the attention of a physician, and the therapist is the first health care professional to observe the skin lesion.

It is important to ask about physical findings in other parts of the body (e.g., the client may not mention genital lesions or may be unaware of the sig-

*Continued.*

**Table 10-2** Effects of Aging on the Skin

Structural	Functional
<b>Epidermis</b>	
Flattening of the dermal-epidermal junction Changes in basal cells Decreased number of Langerhans cells	Altered skin permeability Decreased inflammatory responsiveness Decreased immunologic responsiveness; increased risk of skin cancer; increased sensitivity to allergens Impaired wound healing; loss of photoprotection with increased risk of skin cancer
Decreased number of melanocytes	
<b>Dermis</b>	
Decreased dermal thickness; degeneration of elastin fibers Decreased vascularization	Decreased elasticity; increased wrinkling, slow wound healing, less scar tissue (cosmetic benefit) Decreased vitamin D production
<b>Appendages</b>	
Decreased number and distorted structure of sweat glands Decreased number and distorted structure of specialized nerve endings Decreased hair bulb melanocytes and decreased number of hair follicles	Decreased eccrine sweating; altered skin thermoregulation Impaired sensory perception; increased pain threshold Change in hair color (grey, white); hair loss

nificance of other symptoms). All dermatologic lesions must be examined by a physician, and anyone with evidence of sun damage, particularly those with actinic keratoses (see discussion), should have a full skin examination annually.

## COMMON SKIN DISORDERS

### Atopic Dermatitis

#### Definition and Incidence

Atopic dermatitis (AD) is a chronic inflammatory skin disease. It is the most common type of eczema, frequently already present during the first year of life and affecting more than 10% of children.

AD is considered an early manifestation of atopy that appears before the development of allergic rhinitis or asthma. The word *atopic* (from *atopy*) refers to a group of three associated allergic disorders: asthma, allergic rhinitis (hay fever), and AD. There is usually a personal or family history of allergic disorders present, and AD is often associated with food allergies as well.

#### Etiologic and Risk Factors and Pathogenesis

The exact cause of AD is unknown, although recent studies have demonstrated the complex interrelationship of genetic, physical environment, skin barrier, pharmacologic, psychologic, and immunologic etiologic factors that contribute to the development and severity of AD.<sup>85,159</sup>

The pathomechanisms associated with AD are also unknown but most likely include both immediate and cellular immune responses. Two possibilities include the release of inflammatory mediators by autoallergens and

the release of proinflammatory cytokines by autoreactive T cells in response to autoallergens mediated by immunoglobulin E (IgE).<sup>155</sup>

AD is often associated with increased levels of serum IgE and with sensitization to food allergens.<sup>139</sup> Some foods may be responsible for exacerbations of skin inflammation, but their pathogenic role must be clinically assessed before an avoidance diet is recommended.<sup>68</sup> Xerosis (abnormal dryness) associated with AD is usually worse during periods of low humidity and over the winter months in northern latitudes.

The underlying biochemical abnormality in xerosis is unknown, and the pathologic findings may be a result of the dry skin rather than the cause of the drying effects of this condition. Compared with normal skin, the dry skin of AD has a reduced water-binding capacity, a higher transepidermal water loss, and a decreased water content. Rubbing and scratching of itchy skin are responsible for many of the clinical changes seen in the skin. Hands frequently in and out of water make the condition worse.

#### Clinical Manifestations

AD begins in many people during infancy in the form of a red, oozing, crusting rash classified as acute dermatitis (Fig. 10-4). As the child grows, the chronic form of dermatitis results in skin that is dry, thickened, and brownish-grey in color (lichenified). The rash tends to become localized to the large folds of the extremities as the person becomes older. It is found mainly on flexor surfaces such as the elbows and knees, neck, sides of the face, eyelids, and the backs of hands and feet. Hand and foot dermatitis can become a significant problem for some people.

Xerosis and pruritus are the major symptoms of AD and cause the greatest morbidity with severely excoriated lesions, infection, and scarring. Viral, bacterial, and fungal secondary skin infections may cause further changes in the skin. *Staphylococcus aureus* is the most common bacte-

**Figure 10-4**

Infantile atopic dermatitis with oozing and crusting lesions. (From Paller A, Mancini A: Hurwitz clinical pediatric dermatology: a textbook of skin disorders of childhood and adolescence, ed 3, Philadelphia, 2006, Saunders.)

rial infection, resulting in extensive crusting with serous weeping, folliculitis (inflammation of hair follicles), pyoderma (pus), and furunculosis (boils).

### MEDICAL MANAGEMENT

**DIAGNOSIS, TREATMENT, AND PROGNOSIS.** Although no cure exists, AD often resolves spontaneously, and more than 90% of cases of AD can be effectively controlled through proper management. The goal of medical therapy is to break the inflammatory cycle that causes excess drying, cracking, itching, and scratching.

Personal hygiene, moisturizing the skin, avoidance of irritants, topical pharmacology, and systemic medications (e.g., antibiotics, antihistamines, and rarely, systemic corticosteroids) are treatment techniques currently available. *S. aureus*, known to colonize the skin of people with AD, may exacerbate skin lesions and needs to be treated with antibiotics. Advancing knowledge in understanding the immunologic basis of this disease will continue to result in effective new local and systemic treatments in the decade to come.<sup>104,140</sup>

### SPECIAL IMPLICATIONS FOR THE THERAPIST 10-3

#### *Atopic Dermatitis*

##### PREFERRED PRACTICE PATTERNS

**7A:** Primary Prevention/Risk Reduction for Integumentary Disorders

**7B:** Impaired Integumentary Integrity Associated with Superficial Skin Involvement

The therapist may be instrumental in providing client education that results in avoiding factors that precipitate or exacerbate inflammation and then teaching proper management techniques for flare-ups. Daily care (hydration and lubrication) of the skin is important, and applications (two or three times daily) of emollients that occlude the skin to prevent evaporation and retain moisture should be recommended.

Creams or ointments containing petrolatum or lanolin may be used unless the person is sensitized to lanolin (see the section on Contact Dermatitis), and those that contain urea or lactic acid improve the binding of water in the skin and prevent evaporation. In the case of skin redness, the skin lesion must be identified first because of possible fungal origin requiring an antifungal preparation.

Understanding the individual disease pattern and identifying exacerbating factors are crucial to effective management of this disorder. It is important to identify and eliminate triggers that cause the AD to flare.

Older clients should be encouraged to bathe with tepid water using a nondrying, nonfragranced, or unscented soap or other agent when indicated. Emollients must be applied to the body within 5 minutes after showering or bathing, especially in dry, winter weather, to prevent further skin drying.

Dermatitis must be considered a precaution, if not a contraindication, to some treatment modalities used by therapists. The use of water, alcohol, or any topical agents containing alcohol should be avoided. Topical agents, such as ultrasound gel and mobilization creams, must be used carefully, observing for any skin reaction. A nonreactive response does not guarantee the client will not react when such agents are subsequently applied in future interventions. Caution and careful observation are encouraged.

### Contact Dermatitis

#### Etiologic Factors, Incidence, and Pathogenesis

Contact dermatitis can be an acute or chronic skin inflammation caused by exposure to a chemical, mechanical, physical, or biologic agent. It is one of the most common environmental skin diseases occurring at any age. As people age, they may develop delayed cell-mediated hypersensitivity to a variety of substances that come in contact with the skin.

Common sensitizers include nickel (found in jewelry and many common foods), chromates (used in tanning leathers), wool fats (particularly lanolin found in moisturizers and skin creams), rubber additives (see the section on Latex Rubber Allergy in Chapter 4), topical antibiotics (typically neomycin and bacitracin),<sup>12</sup> and topical anesthetics, such as benzocaine or lidocaine.<sup>57</sup> Dermatitis of unknown cause is more commonly diagnosed in the older population.

A small percentage of the population is allergic to silicone. The therapist is most likely to see this reaction in a sensitized person with an amputation using a silicone type of interface in a prosthetic device (designed to reduce shear, decrease repetitive stress, and absorb shock). Silicone sheets used for scar reduction in the postburn population may also result in an episode of contact dermatitis.

#### Clinical Manifestations

Intense pruritus (itching), erythema (redness), and edema of the skin occur 1 to 2 days after exposure in previously

**Figure 10-5**

Primary contact dermatitis, a local inflammatory reaction, can occur in response to an irritant in the environment or an allergy. Characteristic location of lesions often gives a clue to the cause. Erythema occurs first, followed by swelling, wheals or urticaria, or maculopapular vesicles accompanied by intense pruritus. The example shown here is a result of contact with poison ivy. (From Paller A, Mancini A: Hurwitz clinical pediatric dermatology: a textbook of skin disorders of childhood and adolescence, ed 3, Philadelphia, 2006, Saunders.)

sensitized persons. Clinical manifestations begin at the site of exposure but then extend to more distant sites. These conditions may progress to vesiculation, oozing (watery discharges), crusting, and scaling (Fig. 10-5). If these symptoms persist, the skin becomes thickened, with prominent skin markings and pigmentation changes. Older people have a less pronounced inflammatory response to standard irritants than do younger persons.

## MEDICAL MANAGEMENT

**DIAGNOSIS, TREATMENT, AND PROGNOSIS.** If contact dermatitis is suspected, the client should be referred to a physician. A detailed history and careful examination are frequently all that are needed to make the diagnosis. It may be necessary to perform patch testing to identify the causative agent.

Primary treatment is removal of the offending agent; treatment of the skin is secondary. The client should be instructed to avoid contact with strong soaps, detergents, solvents, bleaches, and other strong chemicals. The involved skin should be lubricated frequently with emollients. Topical anesthetics or steroids (topical or sometimes systemic) or both may be prescribed. For those people unable to avoid known allergens, immunosuppressant therapies (including phototherapy) can be helpful.<sup>20</sup>

Acute lesions usually resolve in 3 weeks; chronic lesions persist until the causative agent has been removed.

## SPECIAL IMPLICATIONS FOR THE THERAPIST

10-4

### Contact Dermatitis

#### PREFERRED PRACTICE PATTERNS

**7A:** Primary Prevention/Risk Reduction for Integumentary Disorders

**7B:** Impaired Integumentary Integrity Associated with Superficial Skin Involvement

The therapy professional should always consider the client's reactions to external substances. This is of particular importance when applying any cream, topical agent, or solution. Various modalities used within the profession may involve causative substances (e.g., whirlpool additives, ultrasound gels, self-sticking electrode pads).

Whirlpools should be used rarely, and with no additives. The client's skin must always be examined before and after intervention for the appearance of any adverse reactions. The client should be instructed to report any discomfort or unusual findings during or after treatment to the therapist.

The person with contact dermatitis associated with the use of a silicone sleeve or interface with a prosthetic device should be cautioned about the use of soaps that do not include a rinsing agent. Many antibacterial and antiperspirant soaps leave particles on the surface of the skin that act as a barrier on the skin's surface against bacterial invasion. A rash or blister may occur in patchy areas corresponding to pressure points when the friction of the interface drives the soap particles back into the skin.<sup>21</sup>

The therapist may suggest one of several care plans for this type of contact dermatitis. The use of alcohol-based lubricants or soaps, antifungal or antibacterial soaps without a rinsing agent, and lanolin should be avoided. Soap-free cleansing agents or a soft soap should be used for daily cleansing, and a petroleum-based ointment can be applied to the limb before putting on the liner.

Water-based ointments should be avoided when using urethane liners, because these can cause the normally tacky urethane to adhere to the skin so that when the liner is removed, bits of skin may be pulled off as well. Alcohol-based lubricants or soaps should also be avoided with urethane products because these components act as a solvent on urethane, increasing the stickiness of the urethane.<sup>21</sup>

## Eczema and Dermatitis

#### Definition and Overview

*Eczema* and *dermatitis* are terms that are often used interchangeably to describe a group of disorders with a characteristic appearance. Eczema or dermatitis is a superficial inflammation of the skin caused by irritant exposure, allergic sensitization (delayed hypersensitivity), or genetically determined idiopathic factors.

Many types of dermatitis are represented according to these major etiologic categories (e.g., allergic dermatitis,