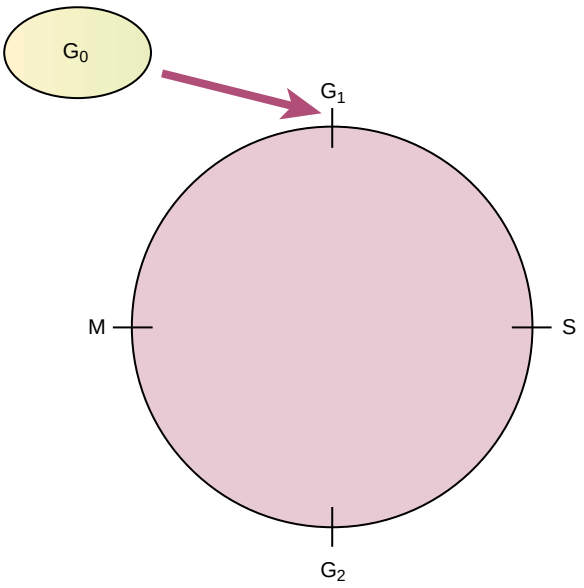

Figure 64–1 Normal cell cycle. The normal cell cycle (the interval between the birth of a cell and its division into two daughter cells) involves several phases. During the resting phase (G_0), cells perform all usual functions except replication; that is, they are not dividing but are capable of doing so when stimulated. Different types of cells spend different lengths of time in this phase, after which they either reenter the cell cycle and differentiate or die. During the first active phase (G_1), ribonucleic acid (RNA) and enzymes required for production of deoxyribonucleic acid (DNA) are developed. During the next phase (S), DNA is synthesized for chromosomes. During G_2, RNA is synthesized, and the mitotic spindle is formed. Mitosis occurs in the final phase (M). The resulting two daughter cells may then enter the resting phase (G_0) or proceed through the reproductive cycle.

body and produce additional neoplasms at sites distant from the primary tumor (metastasis).

A malignant cell develops from a transformed normal cell. The transformation may begin with a random mutation (abnormal structural changes in the genetic material of a cell). A mutated cell may be destroyed by body defenses (eg, an immune response), or it may replicate. During succeeding cell divisions, additional changes and mutations may produce cells with progressively fewer normal and more malignant characteristics. It usually takes years for malignant cells to produce a clinically detectable neoplasm.

CANCER

The term *cancer* is used to describe many disease processes with the common characteristics of uncontrolled cell growth, invasiveness, and metastasis, as well as numerous etiologies, clinical manifestations, and treatments. One theory of carcinogenesis involves abnormal genes and cells, in which cancer may be caused by mutation of genes (abnormal structural changes in cellular genetic material), abnormal activation of genes that regulate cell growth and mitosis, or lack of tumor suppressor genes. The abnormal genes, called *oncogenes*, are mutations of normal growth-regulating genes called proto-oncogenes, which are present in all body cells. Normally, proto-oncogenes are active for a brief period in the cell reproductive cycle. When exposed to carcinogens and genetically altered to oncogenes, however, they may operate continuously and cause abnormal, disordered, and unregulated cell growth. Unregulated cell growth and proliferation increases the probability of neoplastic transformation of the cell. Tumors of the breast, colon, lung, and bone have been linked to activation of oncogenes.

Tumor suppressor genes (anti-oncogenes) normally function to regulate and inhibit inappropriate cellular growth and proliferation. Abnormal tumor suppressor genes (ie, absent, damaged, mutated, or inactivated) may be inherited or result from exposure to carcinogens. When these genes are inactivated, a block to proliferation is removed and the cells begin unregulated growth. One tumor suppressor gene, p53, is present in virtually all normal tissues. When cellular deoxyribonucleic acid (DNA) is damaged, the p53 gene allows time for DNA repair and restricts proliferation of cells with abnormal DNA. Mutations of the p53 gene, a common genetic change in cancer, are associated with more than 90% of small-cell lung cancers and more than 50% of breast and colon cancers. Mutant p53 proteins can also form complexes with normal p53 proteins and inactivate the function of the normal suppressor gene.

Thus, activation of oncogenes and inactivation of anti-oncogenes probably both play roles in cancer development. Multiple genetic abnormalities are usually characteristic of cancer cells and may occur concurrently or sequentially.

Overall, evidence indicates that neoplastic transformation is a progressive process involving several generations of cells, with each new generation becoming more like malignant cells. Thus, malignancy probably results from a combination of factors experienced over a person's lifetime. One factor may be a random cell mutation. However, mutations and malignancies are increased in people exposed to certain chemical, physical, or biologic factors, especially in large amounts or for long periods of time. Some carcinogens and risk factors are listed in Box 64–1. Once a cancer develops, factors influencing the growth rate include blood and nutrient supply, immune response, and hormonal stimulation (eg, in tumors of the breast, uterus, ovary, and prostate).

Classification of Malignant Neoplasms

Malignant neoplasms are classified according to the type of tissue involved, the rate of growth, and other characteristics. With the exception of the acute leukemias, they are considered chronic diseases.

Hematologic malignancies involve the bone marrow and lymphoid tissues; they include leukemias, lymphomas, and multiple myeloma. *Leukemias* are cancers of the bone marrow characterized by overproduction of abnormal white blood cells. The four main types are acute lymphocytic; acute myelo-