the alterations and underlying mechanisms in organ specific diseases such as ischemic heart disease. In this book we first cover the principles of general pathology and then proceed to specific disease processes as they affect particular organs or systems.

The four aspects of a disease process that form the core of pathology are its cause *(etiology)*, the biochemical and molecular mechanisms of its development *(pathogenesis)*, the structural alterations induced in the cells and organs of the body *(morphologic changes)*, and the functional consequences of these changes *(clinical manifestations)*.

Etiology or ***Cause.*** Although there are myriads of factors that cause disease, they can all be grouped into two classes: genetic (e.g., inherited mutations and disease-associated gene variants, or polymorphisms) and acquired (e.g., infectious, nutritional, chemical, physical). The idea that one etiologic agent is the cause of one disease—developed from the study of infections and inherited disorders caused by single genes—is not applicable to the majority of diseases. In fact, most of our common afflictions, such as atherosclerosis and cancer, are multifactorial and arise from the effects of various external triggers on a genetically susceptible individual. The relative contribution of inherited susceptibility and external influences varies in different diseases.

Pathogenesis. ***Pathogenesis*** **refers to the sequence of cellular, biochemical, and molecular events that follow the exposure of cells or tissues to an injurious agent.** The study of pathogenesis remains one of the main domains of pathology. Even when the initial cause is known (e.g., infection or mutation), it is many steps removed from the expression of the disease. For example, to understand cystic fibrosis it is essential to know not only the defective gene and gene product, but also the biochemical and morphologic events leading to the formation of cysts and fibrosis in the lungs, pancreas, and other organs. Indeed, as we shall see throughout the book, the mutated genes underlying a great number of diseases have been identified, but the functions of the encoded proteins and how mutations induce disease—the pathogenesis—are still not fully understood. With more research into clinical genomics it may become feasible to link specific molecular abnormalities to disease manifestations and to possibly use this knowledge to design new therapeutic approaches. For these reasons, the study of pathogenesis has never been more exciting scientifically or more relevant to medicine.

Morphologic Changes. **Morphologic changes refer to the structural alterations in cells or tissues that are either characteristic of a disease or diagnostic of an etiologic process.** Traditionally, the practice of diagnostic pathology has used morphology to determine the nature of disease and to follow its progression. Although morphology remains a diagnostic cornerstone, its limitations have been evident for many years. For example, morphologically identical lesions may arise by distinct molecular mechanisms. Nowhere is this more striking than in the study of tumors; breast cancers that are indistinguishable morphologically may have widely different courses, therapeutic responses, and prognosis. Molecular analysis by techniques such as next generation sequencing (Chapter 5) has begun to reveal genetic differences that predict the behavior of the tumors as well as their responsiveness to different therapies. Increasingly, targeted therapies based on molecular alterations are being used for the treatment of cancers. Hence the field of diagnostic pathology has expanded to include molecular biologic and proteomic approaches for analyzing disease states.

Functional Derangements and Clinical Manifestations. The end results of genetic, biochemical, and structural changes in cells and tissues are functional abnormalities, which lead to the clinical manifestations (symptoms and signs) of disease, as well as its progress (clinical course and outcome). Hence, clinicopathologic correlations are very important in the study of disease.

Virtually all forms of disease start with molecular or structural alterations in cells. This concept of the cellular basis of disease was first put forth in the nineteenth century by Rudolf Virchow, known as the father of modern pathology. We therefore begin our consideration of pathology with the study of the causes, mechanisms, and morphologic and biochemical correlates of *cell injury*. Injury to cells and to extracellular matrix ultimately leads to *tissue and organ injury*, which determines the morphologic and clinical patterns of disease.

Overview: Cellular Responses to Stress and Noxious Stimuli

The normal cell is confined to a fairly narrow range of function and structure by its state of metabolism, differentiation, and specialization; by constraints of neighboring cells; and by the availability of metabolic substrates. It is nevertheless able to handle physiologic demands, maintaining a steady state called *homeostasis*. *Adaptations* are reversible functional and structural responses to changes

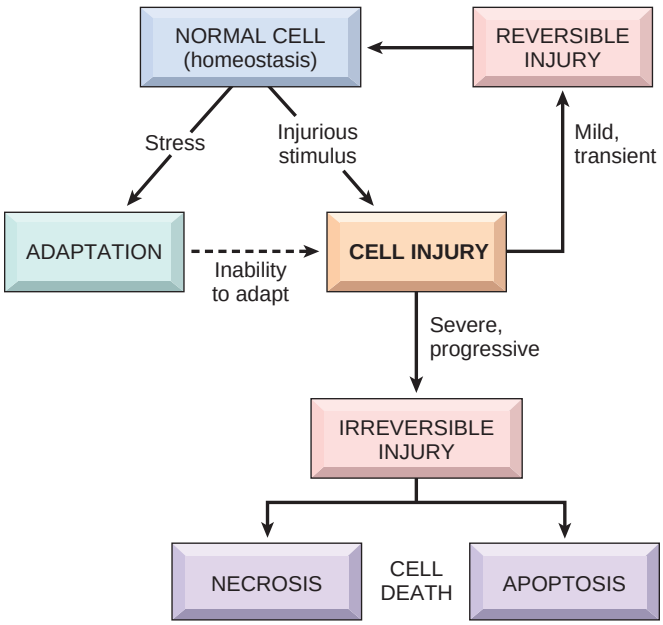

Figure 2-1 Stages of the cellular response to stress and injurious stimuli.

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