CHAPTER 1

BIOMARKERS: AN EVOLUTIONARY PERSPECTIVE

Michael A. Ferguson and Vishal S. Vaidya

The official National Institutes of Health (NIH) definition of a biomarker (biologic marker) is "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention." This definition is broad and, though not explicitly stated, encompasses laboratory tests, radiologic studies, as well as physical exam findings. Although the term biomarker is a relatively new one that dates back to the late 1960s, biologic assessments and measurements in the evaluation of human disease were practiced in antiquity, evident in the writings of the ancient Egyptians. Not surprisingly, clinically useful biomarkers have evolved over time, reflecting the scientific and technologic progress made over the centuries (see Figure 1.1). As a result, an increasing number of clinically relevant tests and procedures are available to estimate organ injury and guide treatment. Recent discoveries in genetics and molecular biology have resulted in impressive advances in our understanding of the pathophysiologic processes of individual diseases and yielded an abundance of prospective therapies directed against novel targets. This has brought about an increased focus on biomarker identification, validation, and quantification, as well as the development of analytical technologies for biomarker measurement. It is anticipated that further characterization of novel biomarkers will enable improvements in diagnostic and prognostic strategies and facilitate accelerated development of new pharmacologic and non-pharmacologic therapies, ultimately resulting in improved patient outcomes.

In their earliest incarnation, biomarkers were confined to objective physical findings and observations, such as heart rate and tactile temperature and general features of the patient's body. The diagnostic and prognostic utility of such physical biomarkers can be traced to the earliest known medical manu-
The evolution of biomarkers in medicine. Through the centuries, biomarkers have taken on different forms. Physical indicators of health and disease were the earliest biologic markers, dating back to the seventeenth century B.C. Qualitative analysis of biologic fluids followed, with uroscopy representing the major diagnostic modality employed from the sixth century B.C. through the eighteenth century A.D. Clinical chemistry and microscopy altered the scope of laboratory specimen and allowed for the routine assessment of analytes in bodily fluids in twentieth century medicine. The twenty-first century has brought with it the emergence of "omic" technologies, vastly increasing the number of biomarkers in medicine.

scripts, the medical papyruses of ancient Egypt (seventeenth century B.C.). The Edwin Smith Papyri, believed to be written around 1500 B.C. and based on the earlier work of Imhotep (twenty-seventh century B.C.), details 48 cases of trauma as well as therapeutic and prognostic considerations. Breasted's translation of this document reveals "an ancient Egyptian surgeon... as a man with the ability to observe, to draw conclusions from his observations... and maintain a scientific attitude of the mind." The examination of biologic specimens can also be traced to ancient times, with reference to the qualitative inspection of urine and stools referenced in the Assyrian Book of Prognoses (650 B.C.). Not surprisingly, the prognostic and diagnostic significance of findings around this time was based on a combination of observation and spiritual mysticism.

The utility of biologic specimens in the diagnosis and prognosis of disease was further advanced by the ancient Greeks. Hippocrates (350 B.C.) advocated a systematic approach to the patient that included physical exam procedures as well as careful inspection of bodily fluids. The Hippocratic physician employed his five senses to study the patient's secretions and excretions to determine the prognosis of a disease and aid in treatment. Par-
ticular emphasis was placed on the evaluation of urine, and Hippocrates is credited with relating specific urinary characteristics, including sediments and surface foam, to chronic illness. In the centuries that followed, the practice of uroscopy became paramount in patient evaluation, and by the Middle Ages the mutua (urine flask) emerged as the most recognizable symbol of medical practitioners. The importance of urinary diagnosis became exaggerated in the seventeenth century when it often superseded direct evaluation of the patient, leading to isolation of the physician and patient. This resulted in a backlash against those who practiced uroscopy; however, macroscopic examination of the urine remained the primary biologic marker in clinical diagnosis until the Victorian era.

The nineteenth century brought impressive advances that allowed for the generation of increasing amounts of clinical data. Instruments, such as the stethoscope, ophthalmoscope, laryngoscope, spirometer, electrocardiogram, and sphygmomanometer, allowed for improved physical exam assessment and physiologic measurement. In addition, the X-ray, microscope, as well as new laboratory-based chemical and microbiologic techniques, vastly expanded the physician's diagnostic capabilities. These developments allowed for an unparalleled degree of objectivity with respect to the assessment of biologic indicators of normal and abnormal biologic function. As a result, physicians were able to establish standards and evaluate deviations of human physiology.

By the turn of the twentieth century, clinical laboratories were growing in favor and influence and clinico-pathological laboratories opened in an increasing number of hospitals. Systematic analysis of blood and urine samples established reference levels for a variety of analytes, correlated variations in disease states, and clarified metabolic pathways in health and disease. Advances in analytic techniques, including chromatographic separation and colorimetric quantification of analytes, facilitated clinical usefulness and resulted in the ability to assay a growing number of biologic markers to monitor the changing condition of the patient. Increasingly, the medical provider became dependent on the chemical analysis of bodily fluids in the monitoring of health, diagnosis, and prognosis of disease, and assessment of response to therapeutic interventions. With increased understanding of the pathophysiologic processes involved in specific disease processes, the quest to identify and characterize biologic markers with improved sensitivity and specificity for a variety of illnesses and associated outcomes has followed.

Efforts at biomarker discovery and validation have intensified since the turn of the twenty-first century. Advanced genomic, proteomic, and metabolomic techniques now permit comparative analysis of specimens from healthy and diseased individuals, facilitating biomarker identification. As a result, biomarker initiatives have become ubiquitous in the scientific landscape, with considerable private and public resources now dedicated to clarifying the utility of biologic markers in virtually all aspects of health care. Novel measures of biologic function will prove critical in the research setting, serving as surrogate endpoints in clinical trials that promise to streamline pharmacologic and non-pharmacologic therapeutic development. In addition, it is anticipat-
ed that selected biomarkers and/or biomarker panels will revolutionize drug development, environmental health screening, and medicine, facilitating the movement toward personalized patient care. Ongoing and future biomarker studies are likely to enable individualized assessment of disease susceptibility, response to therapy, as well as disease progression/regression. An emphasis on concurrent development of technologies for rapid biomarker analysis, ideally point of care modalities, will help ensure rapid assimilation into clinical practice.

The use of biologic measures in the assessment of health and disease is not new; however, the concept of what constitutes a useful biomarker has evolved considerably, closely paralleling technologic advances of the time. The current era of scientific discovery has brought seemingly limitless opportunities for improvements in medical care. Coordinated efforts at biomarker discovery and validation, as well as technologies for biomarker measurement, will help ensure that the ultimate goal of safer drugs, a cleaner environment, and improved patient outcomes is realized.

REFERENCES