The etiopathogenesis of neoplastic diseases is characterized by its multiple nature. Biological, chemical, and physical agents have been identified as initiating or promoting neoplastic mechanisms. However, they all appear to have a common molecular basis, granting genetic instability and causing somatic derangements to pre-neoplastic and tumor cells. In addition to these somatic mutations, which are the most frequent abnormalities identified in human cancer, germ-line mutations associated with specific familial cancer syndromes have also been characterized. Epidemiologic and molecular genetic studies have unveiled the underlying mutations of specific genes predisposing patients to distinct cancers, such as certain colorectal and breast tumors. It is therefore conceivable to view cancer as fundamentally a genetic disease entailing germ-line and somatic mutations. However, epigenetic events and altered patterns of protein expression have been also identified in neoplastic lesions, and their identification has become as important in the context of certain tumor classification schemes, as well as in the predicting course of disease.

Alterations in proto-oncogenes and tumor suppressor genes seem equally prevalent among human cancers. Multiple mutations appear to be required to conform the malignant phenotype. Genetic instability leads to a sequence of events that creates phenotypic alterations, granting a selective advantage to specific tumor cells. Metastasis is the ultimate outcome of tumor progression in this selective process. It appears that it is the accumulation rather than the order of these pleiotropic events that confers neoplastic cells the ability for tumor progression.

Tumors are composed of heterogeneous populations of neoplastic cells with different morphologies and phenotypes. The existence of the cancer stem cell has been postulated, this cell being responsible for tumor initiation and giving rise to differentiated progeny, thus capable of generating the heterogeneity observed in tumors and the hierarchical state of these lesions. The identification of this ‘cancer stem cell’ population has important implications for the management of cancer patients. This includes diagnostic and predictive laboratory assays, as well as novel therapeutic strategies specifically targeting the cancer stem cell. Combination of this new therapy with current treatments that target the differentiated, expanding tumor cell subpopulations should eradicate tumors more efficiently, reduce the risk of relapse, and impact on metastatic clones and tumor resistance to conventional therapies. Many characteristic properties have been attributed to stem cells, there are two cardinal features: they are (a) capable of self-renewal, producing new stem cells through cell division, and (b) multipotent progenitors that can give rise to differentiated transient amplifying cells through asymmetrical cell division. The cancer stem cell model proposes that cell populations within a tumor have a hierarchical organization, in which a stem cell-like population gives rise to more differentiated derivatives that lack tumor initiating and/or long-term self-renewal capability. This view is consistent with the observed phenotypic heterogeneity found in many tumors. In contrast, a stochastic model of tumor development suggests that the phenotypic heterogeneity of tumors is simply due to variations in the genetic or epigenetic composition of tumor subpopulations, but that these subpopulations have similar tumor initiating ability under appropriate circumstances. Experimental assays for identification of cancer stem cells in human tumors have generally involved xenotransplantation, and many published studies have reported the identification of rare tumor-initiating cells in a range of cancers. However, recent work has questioned the interpretation of these studies, since technical improvements in xenotransplantation assays can yield significant increases in xenotransplantation efficiency to the point where as many as 25% of melanoma cells can display tumor-initiating properties. The novel cancer stem cell model has strong translational and clinical relevance, since it can explain many of the features of resistance to cancer therapy. In particular, conventional therapeutic approaches usually target cellular proliferation, yet the cancer stem cell population may be relatively resistant due to its lower proliferative rate. Thus, identification of cancer stem cells would likely have several translational implications for cancer treatment. First, the identification of markers for cancer stem cells would allow the correlation of tumor-specific stem cell status in tumors with histopathology and clinical outcomes, and might also serve as accurate surrogate measures for the efficacy of cancer treatments. Secondly, the cancer stem cell model can potentially account for the metastatic potential of a tumor, since the ability of circulating tumor cells to generate a secondary metastasis presumably requires the presence of a self-renewing progenitor, or cancer stem cell. Consequently, the assessment of cancer stem cell numbers and molecular properties in a particular tumor may have prognostic value for the risk of metastatic disease. Finally, the identification and molecular characterization of this cancer
stem cell population may lead to future targeted therapeutic interventions.

The diagnosis of cancer and assessment of its management is entering an era in which immunopathology and molecular genetics could play important roles. During the past years a tremendous amount of information has been generated regarding the principles that govern cell growth, cell senescence, and cell death (‘apoptosis’) itself. Combinations of abnormalities in these processes are important not only for causing prostate cancer, but also for permitting or inhibiting prostate tumor cells to respond to therapeutic interventions. Clinical trials have shown different responses to various therapies that correlate with molecular alterations. Biological determinants related to treatment response and markers aimed at individualized therapies are being defined and implemented. It is expected that the newly developed high-throughput methods, such as expression profiling by microchip technology, will complement our armamentarium of predictive tools needed to address the molecular complexity that characterizes prostate cancer.

In addition to molecular genetics, a new ‘systems pathology’ approach is being developed. Systems pathology can be defined as a discipline that integrates clinical variables with histological and cellular features, as well as molecular profiles. This is achieved through the application of novel technologies in the areas of object-oriented image analysis, pattern recognition, and quantitative biomarker multiplexing. The obtained complex data-sets are analyzed by distinctive supervised mathematical approaches, including machine learning algorithms and neural networks. Our working hypothesis is that by using this approach we could significantly improve the accuracy of predictive tools, such as individualized nomograms already developed for the management of prostate cancer.

The practice of conventional histopathology based on light microscopy changed and was in part complemented in the second half of the twentieth century by three technological advances: ultrastructure, immunohistochemistry, and molecular diagnostics. The first two represented incremental gains in diagnostic power and efficiency, but did not force substantial changes in the practice of morphological studies. However, ‘molecular medicine’ is profoundly changing the approach to tissue analyses. Perhaps more importantly, molecular medicine is altering the pathway for advancement. In the recent years the elucidation of the molecular pathogenesis of neoplastic diseases and the multistep nature of cancer progression has directly led to the discovery and application of molecular tumor markers. The diagnosis and prognosis have in many cases been enhanced by the use of the marker(s), and finally the marker may constitute a therapeutic target (e.g. HER-2/neu and Herceptin, Bcr-Abl and Gleevec). The advances in biotechnology and bioinformatics is making possible the integration of these novel diagnostic and therapeutic approaches. Moreover, the preceding sequence of events can be predicted to accelerate. Rather than elucidating a molecular pathway, we will have a complete view of the molecular genetics and protein profile of a given tumor. This comprehensive understanding will lead to the development of specific therapies and to the rational selection of therapeutic modalities for a specific patient. Integrated tests will allow an accurate assessment of the response and modification of therapy when required. The detailed morphologic and molecular knowledge of the natural history of tumors will yield markers for inherited and acquired risks, tumorigenesis and tumor progression. These will in turn make early diagnosis and cancer monitoring a reality. These issues will be discussed during the lecture.