monitor people undergoing treatment, many of those used as cancer biomarkers are inaccurate. For example, prostate-specific antigen (PSA) can give false positives because this antigen can be elevated in blood for other reasons.

Circulating DNA (ctDNA) in human blood, first reported in the blood of cancer patients in 1977, might perform better than proteins as a biomarker because it bears mutations that are hallmarks of cancer.[19] Circulating tumor DNA is composed of genome fragments that are released when cancer cells die and float freely through the bloodstream, and it could be an excellent cancer biomarker. Unfortunately, ctDNA is not yet ready for a leading role in the clinic, mainly because the most sensitive techniques for its detection require some knowledge about which mutations to search for, and this is a laborious task that must be performed for each individual patient. One alternative is to use exome sequencing, which does not require a previous knowledge about the cancer but is prohibitively expensive. A focused approach to the therapy of lung cancer that would permit keeping costs low has been developed. This approach is based on the identification of a small fraction of the genome (0.004%) that is repeatedly mutated in these cancers. Because almost all patients with lung cancer have at least one mutation in these regions, these mutations may be found by sequencing this small fraction 10,000 times over. The method should work in almost every cancer, except in the case of brain cancers, in which the blood–brain barrier stops tumor DNA from reaching the bloodstream. Unfortunately, the potential of ctDNA as a cancer-screening tool is limited to advanced forms of cancer, which discharge relatively high levels of DNA, but it does not perform well for detecting early cancer forms.[20] It is likely that molecular characterization of a given cancer will lead to the identification of different subsets of cancer disease with a different natural history, sensitivity, and resistance to treatment. In this task, efforts to develop, validate, and implement predictive biomarkers in clinical trials and eventually in routine care are important.

Despite the current emphasis on the early diagnosis of cancer, statistical data demonstrate that advances in this field have not led to a proportional decline in later stage disease.[21] Emphasis on early diagnosis of cancer may lead to overdiagnosis—that is, the detection of tumors that if left unattended would not become clinically apparent or cause death. To minimize overdiagnosis of cancer, some oncologists have proposed a change in terminology, with the term “cancer” reserved only for lesions with a reasonable likelihood of lethal progression if left untreated.

4 A BRIEF HISTORY OF CANCER CHEMOTHERAPY

In addition to biological knowledge, chemistry has had varying roles in the discovery and development of anticancer drugs since the beginning of cancer therapies.[22]

Modern cancer chemotherapy has its origin in the development of nitrogen mustards as chemical weapons. Since those early years, synthetic chemistry has been extensively used to modify drug leads, especially those of natural origin, and to solve the problem of the often scarce supply of anticancer natural products by developing semisynthetic or fully synthetic strategies.

The first cytotoxic agents, most of which are still used in the clinic, were discovered through different approaches, although their mechanism was unknown. The synthesis of folate analogs was undertaken following the observation that folic acid stimulates the proliferation of acute lymphoblastic leukemia (ALL) cells, which led to the discovery of methotrexate, the first drug that induced remission in children with ALL. It is interesting to note that the development of resistance induced by old drugs such as nitrogen mustards and methotrexate was apparent since the earliest studies.