Chapter 4
Carcinogenesis
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Introduction

Carcinogenesis is the process that determines the evolution of cancer and it is triggered from mutations in the DNA of normal cells. The resulting alteration in the equilibrium between proliferation and programmed cell death leads to uncontrolled cell division and, therefore, tumor formation. Before the arrival of biomolecular techniques, which revealed that cancer is a pathology with genetic origins, there were various hypotheses regarding the etiology of this complex disease.

Historical Notes

The discovery of cancer has very deep roots in the history of humanity. The first hypothesis, valid until the Modern Era, was inherent in the Galenic-Hippocratic theory, which established that human health depends on an equilibrium of the four “humors” (blood, mucus, and yellow and black bile). The tumor was thus a tangible expression of a grave humoral disturbance (provoked, for example, by a local concentration of black bile), and its excision would eliminate any consequences of the illness but would not completely resolve the disease. Surgical removal of the tumour was merely symptomatic. Instead, the aim of treatment was to restore the internal humoral equilibrium, as indicated by Galeno. This view was confirmed by the observation of the disease course, as tumor-related illness was often fatal and not influenced by surgical interventions. In the 16th–17th century, the humoral theory was still very much accepted. Fabricius Hildanus (1560–1634) [1], one of the Fathers of German surgery and author of the six-volume work, “Observationum et curationum chirurgicarum centuriae”, (Fig. 4.1), analyzed the causes of unsuccessful surgery, above all in the treatment of tumours. In addition to pointing out insufficient technique, he stigmatized the lack of general cognition of medicine among surgeons: “poorly educated and reckless as they are, they do not take into consideration and do not treat the humoral problem, the fundamentals of the growth of tumours!”
Signs of change developed in the 18th century, when the famous English surgeon Percival Pott (1714–1788) posed the question: How does cancer arise? Almost 100 years later, A.W. Volmann was able to correlate environmental factors (skin contact with asphalt and black smoke) with the occurrence of tumors. This was followed in the 19th century by the insights of Muller and Virchow into carcinogenesis. Rudolph Virchow, in his “Die Cellular pathologie”, (1858), translated into English in 1860, first observed that new cells always come from pre-existent ones ’omnis cellula e cellula’ (every cell from cell). He demonstrated that cancerous cells do not exist in and of themselves, regardless of how large or widespread the tumor may be; rather, it arises from a normal cell. The cancerous cell is not strange to our organism; it is a mutated, degenerate cell and therefore, can originate, at any time, from a very small cellular alteration.

In 1915, the Japanese researchers K. Yamagiwa and K. Ichigawa were able to experimentally reproduce tumors in laboratory animals. H.A. Gaylord (1906) hypothesized that tumors were of autoimmune origin. He observed that mice, infected with tumor cells, healed spontaneously, rejecting the carcinogenic cells upon subsequent inoculation, or became resistant. Further progress was made based on the work of the biologist T. Boveri, who demonstrated that in tumor cells, alongside the usual diploid configuration, abnormal mitotic figures, often tetraploid, at times even polyploid and irregularly distorted, could be seen during cell division. These observations gave rise to “the hypothesis of chromosome mutations.” In 1920, R.C. Whitman and K.H. Bauer proposed the “theory of