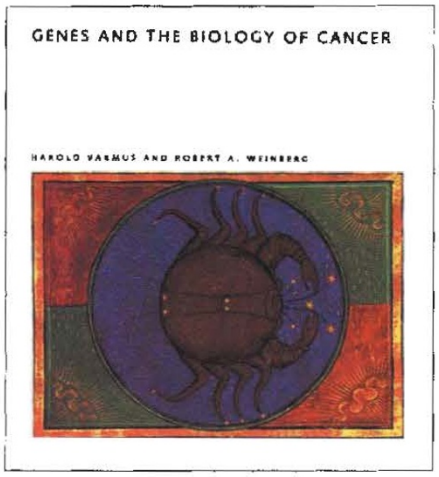

Genes and the Biology of Cancer

by Harold Varmus and Robert A. Weinberg
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For most of this century cancer has been a major subject of concern and investigation. Altogether amazing is the coherent picture of this terrible and fascinating disease that has recently emerged. Theories of its origin have abounded, but those concerning viruses and somatic mutations have held center stage. Over the past twenty years a revolution has provided a stunning array of facts that have brought these two theories together and have focused attention on the central role of mutations in two kinds of genes whose normal function is the regulation of cell multiplication. As with all revolutions there is a wonderful story to tell, but few individuals to tell it compellingly. Two such persons are the authors of this volume.

Harold Varmus and Robert Weinberg, two of the principal architects of this revolution, have undertaken to tell its story to the "motivated but non-expert" reader in eight well-considered chapters. In order to reach as many readers as possible they begin with first principles of the biology of the cell, an essential prelude. Features of the cycle of cell replication, cellular differentiation and maintenance of renewal tissues complete the excellent preparatory first chapter.

The nature of the beast and its causes occupy the reader through two chapters. Virchow's pronouncements about the origin of cells from cells led ultimately to the study of growth of cancer cells in the laboratory. Although cancers arise in many different tissues, they resemble each other in many respects. A historical perspective introduces the reader to external agents that convert normal cells into cancer cells. There is a generous sprinkling of the names of key investigators of the past in the third chapter, including Boveri and his somatic mutation hypothesis, Rous and his tumour virus, and Muller and the discovery of the mutagenicity of X-radiation, already known to be carcinogenic. The authors give a nice description of inconsistencies between the carcinogenic and mutagenic effects of chemicals that cast doubt on the somatic mutation hypothesis, until Ames devised a test that permitted activation of procarcinogens to mutagens in a bacterial test system. The stage was set for discovery of the critical genes that were mutated by radiation and chemicals, and that were provided by, or activated by, certain viruses.

The core of the book is devoted to the subject that is central to the cancer revolution and to which the authors have contributed so much. The discovery of the *src* oncogene of the Rous sarcoma virus and of the *src* proto-oncogene of normal cells (by Bishop, Varmus, and their colleagues) provided entry to the treasure chest of genes whose exaggerated or abnormal activity pushes cells through the cell cycle inappropriately. Then it was realized that proto-oncogenes could be activated or mutated without the intervention of viruses, and that they can become 'cancer genes'. The first oncogenic transformation of a cell *in vitro* by such a mutant proto-oncogene was accomplished by Weinberg, the second author of the present volume. (This reviewer's only regret about the book is that the direct role of the authors in this critical research is not stated.) This chapter nicely discusses the protein products of some proto-oncogenes and their roles in cell physiology. The presentation of the ideas in this chapter (indeed, throughout the book) is helped by the excellent illustrations.

The companion core chapter discusses the tumour suppressor genes, whose normal function is to suppress growth; loss of the activity of such a gene constitutes a second mechanism of carcinogenesis, much as loss of brakes can cause a runaway car. The retinoblastoma gene was the first such gene to be cloned, in Weinberg's laboratory. Inheritance of a mutant tumour suppressor gene can place a person at high risk of cancer and can lead to inherited cancer. The authors tie the action of this class of gene to that of proto-oncogenes through their physical interaction in cells: the same effect might be caused by mutation in either one. This then leads in the sixth chapter to a consideration of the circuitry governing control of growth in normal and cancer cells. In the penultimate chapter the authors skillfully bring these findings from molecular and cell biology together with diverse facts from tumour biology, experimental carcinogenesis, the epidemiology of cancer, and hereditary cancer, leading to a discussion of the multistage nature of cancer that ends ultimately with the spread of tumour cells to sites far beyond their tissue of origin. The story is told well and beautifully illustrated.

Now, the final question for the final chapter: what can we do with this new knowledge to reduce the burden of cancer through prevention and treatment? In some instances, preventive measures are being implemented, as with certain environmental agents, including asbestos and the hepatitis B virus, but for cigarette smoking there is still a terrible cancer toll. The new knowledge of cancer is not central to these efforts, but it is already being applied to improved, and earlier, diagnosis. The real question concerns the possibility that new therapeutic approaches may be developed. This is particularly important, since it is unlikely that we shall ever prevent all cancer.

This book was published in 1993, but the consequence of late review is that it provides the test of durability. At a time when even the expert can be overwhelmed by the onrushing flood of knowledge, the need for organization is enormous. This slender and very readable volume provides that organization, and offers a great opportunity for all students and practitioners of medicine, in fact all scientists, to share in the excitement that currently surrounds a disease that touches all of our lives.