Chapter 1

Genetics and Etiology of Human Cancer

Alfred G. Knudson, Jr.

University of Texas Health Science Center
Houston, Texas 77030

INTRODUCTION: THE ETIOLOGY OF HUMAN CANCER

One of the highest national priorities that has been established for biomedical science in the United States is the control of cancer. Whether that control be achieved through prevention or through treatment, it will probably necessitate a better understanding of the etiology, pathogenesis, and pathophysiology of cancer than is current. In the process of investigation we should also be aware of man's mortality and the possibility that cancer is an intricate part of that larger, uncontrollable problem. To the extent that cancer is caused by spontaneous, time-dependent changes, such as may accumulate from somatic mutation, prevention is a cruel dream; to the extent that cancer is accelerated by controllable environmental agents, prevention is a realistic hope. Clearly, we need to have a firm understanding of the etiology of cancer and of the interaction of genetic and environmental factors involved therein.

Any account of the etiology of cancer must embrace numerous pieces of information gleaned from both man and animal. Hereditary and environmental cancers in man were already known in the last century, and to these, early in this century, were added not only more examples in man but also a major new class, viral, in animals. In one sense there has been little change in this state of affairs in the past 50 years. We still
do not have any clearly viral cancers in man, but we have numerous examples of hereditary cancer and of cancers associated with physical and chemical agents. But there is a far greater understanding of the mechanisms by which these factors operate, and we begin to comprehend the relationships among these mechanisms.

One factor that has been difficult to incorporate is time. The most characteristic feature of human cancer is its age dependence. Each cancer has for a particular population a strongly age-specific incidence. Thus some cancers have a peak incidence in childhood and are rare in adulthood, while many virtually never occur in children and have a steadily rising incidence with age. Even when a cancer is hereditary, it displays a strong age dependence, often with a long latent period. So too for environmental cancers there is a latent period, followed by an age-specific incidence that is dependent on both the agent and the site of the tumor it causes.

Early in the study of cancer it was considered that it is a disease originating in an abnormal cell: the cells of a cancer are usually distinctly abnormal in appearance and resemble each other strongly. Further impetus to this idea came from the observation that the number of chromosomes is abnormal in most cancers. The notion that this abnormality might be basic to the disease and the implications of that notion were articulated forcefully by Boveri,31 who himself never studied cancer but who was the first to suggest the functional individuality of chromosomes, on the basis of his experiments with abnormal embryogenesis in sea urchins. As noted by Wolf,313 Boveri indicated that the abnormal mitoses which he believed could lead to cancer were more likely to occur (1) in tissues induced to undergo heavy proliferation, (2) in aging cells, (3) in cells exposed to X-rays or certain chemicals, and (4) in genetically predisposed individuals. Cancer was visualized as originating in a specific genetic change in one cell of a population of dividing cells.

To this day we do not know whether chromosomal abnormality is a necessary condition for all cancers, although it does seem to be a sufficient condition for some. One requirement imposed by Boveri, that cancer shall have a clonal origin, has been established for many cancers.75,98,176 This conclusion is based on the observation that the normal tissues of females heterozygous at the X-linked glucose-6-phosphate dehydrogenase locus are mosaic, whereas their neoplastic