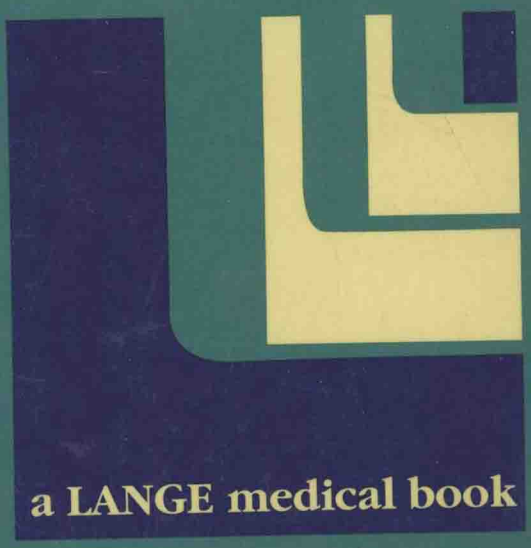
Clinical Oncology

Geoffrey R. Weiss



a LANGE medical book

Clinical Oncology

Edited by

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Preface

The clinical and scientific disciplines that collectively contribute to the field of oncology span nearly all the disciplines of medicine and surgery. Few other areas of human endeavor draw from so many other knowledge bases and offer the opportunity for a fundamental understanding of mechanisms of disease and human biology. Perhaps it is for these reasons that those of us privileged to participate in the intellectual challenges of seeking the causes, prevention, and cure of cancer feel that this is where the action is. Indeed, the scope of the problem is so large that traditional divisions of clinical and scientific labor are giving way to new liaisons and collaborations. The concept of translational science, that is, the application of basic science discoveries to the clinical problems at the bedside, has become one of the imperatives of the oncologist.

In ten years of medical education, I have been struck by the dichotomy between the sense of scientific adventure offered to "students" of the oncologic disciplines and the sense of intimidation felt by physicians-in-training when confronted by problems related to cancer. The custodians of the knowledge related to the care of the cancer patient are viewed as individuals steeped in the problems of death, using poisonous drugs by their order alone, and sequestering their patients in special units with special rules understood only by the initiated. This new text seeks to reduce the mystery of this strange fraternity.

During the past decade, many excellent textbooks and handbooks devoted to the cancer problem and the care of its victims have emerged for use by the medical community. This text has been written to bridge some of the remaining gaps in communicating the cancer knowledge base, particularly for the physician-in-training, the graduate physician, the nonspecialist physician, and other health care professionals. We have assembled a distinguished group of authors to present a readable foundation in oncology for this audience. It is hoped that the effort will result in a tool useful in the clinic and as an introduction to more sophisticated areas of oncology. I welcome comments and criticisms, which I hope will lead to future editions even more useful and topical for readers of this work.

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San Antonio, Texas
May 1993

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Table of Contents

Section I.
Cancer Biology & Etiology

The Cancer Problem 1

Geoffrey R. Weiss, MD

Cancer remains a hugely expensive public health problem in the USA, both in economic terms and in terms of the amount of human suffering it produces. The past two decades have witnessed an explosion in the understanding of the molecular basis of malignant disease and in the rapid application of basic research concepts to the clinical arenas of diagnosis and treatment. Yet the excitement accompanying this new wisdom belies the stubbornness and tenacity with which cancer has resisted satisfactory control. Cancer has been the second leading cause of death in the USA for decades. Although heart disease leads cancer by more than 300,000 deaths per year, cardiovascular deaths are declining, a realization that has led some to project that cancer deaths will predominate by the turn of the century.

Cancer incidence exceeded 1 million cases for 1992. Of that number, one-half died. While half of cancer patients may expect to be cured, the sobering fact remains that the investment of billions of dollars in cancer research, particularly after passage of the National Cancer Act during the Nixon administration, has produced few discoveries having important impact on patient survival for the dominant cancers of the population. Can expenditure of this magnitude against such a daunting foe with so few tangible dividends be rationalized any longer? It may be instructive to examine the cancer problem in ways that elucidate its many facets and suggest that true advances have been made which are not easily measured in terms of cancer patient survival.

Cancer etiology intuitively represents a place to begin applying the resources necessary to solving the cancer problem. But the causes of cancer are multifold and may be viewed from perspectives spanning several orders of magnitude. For the epidemiologist, the problem is one of the human condition, reflecting the tension between environment and genetics. In Western industrialized nations, the impact of culture, habits, diet, and occupation may far exceed the effects of infection, sanitation, natural environment, and heredity that underlie the causes of cancers in less developed or Third World nations. The tasks for the cancer epidemiologist are the identification of those environment determinants of cancer and the alteration of behavior in favor of reducing cancer risk for the population of interest. The well-known determinants of cancer risk for Western or industrializing societies include tobacco consumption, diets high in fat and low in unrefined starches, and occupational exposure to radiation or toxic chemicals.

For the cancer biologist, the problem is viewed at the molecular level, biochemical level, chromosomal level, or cellular level in terms of perturbations of cell homeostasis that result in uncontrolled cell growth and division and the assumption of immortality by the cancer cell. The advances in these arenas have been real, exciting, and potentially prophetic for understanding not only cancer etiology but also normal cell growth and regulation. The discovery of oncogenes, tumor growth factors, chromosomal markers of disease, among others, as new foci for potentially arresting the development of the malignant cell has sparked the interest and imagination of basic scientists and clinicians alike. Conversion of a proto-oncogene to an oncogene may require only a single DNA base pair change coding for a single amino acid alteration in the gene product. Further, genes that suppress an otherwise universal ability of normal cells to assume malignant behavior may undergo mutation or loss under cellular or environmental mechanisms yet to be defined. Such events drive home the realization that all normal cells harbor the potential for becoming promptly malignant as a result of very limited and highly specific changes to the genome and cell machinery. Although the application of these concepts to the predicament of the cancer patient may seem at first far flung, it is becoming clear that many of these basic research techniques can be applied to clinical cancer management: detection of oncogenes in malignant tissues may be associated with poor prognosis for the afflicted host; specific chromosomal aberrations in malignant tissues may permit prediction of poor response to treatment among patients with the same types of leukemia or lymphoma. Now more than ever, advances in the understanding

of cancer biology may importantly contribute extraordinarily potent methods of altering the headlong progression of the malignant engine toward the destruction of the host.

For clinicians, the problem remains the struggle to avert the destruction of the patient by the unrelenting displacement of normal homeostasis accompanying malignant tumor growth, a struggle that all too often is fatal for the cancer patient. The clinical skills necessary to achieve the limited success possible in this era demand the use of destructive agents in a way that straddles the fine line between death of the malignant cell and preservation of the normal cell. The empiricism of the last 20 years in the use of anticancer drugs, radiation, and surgery is being displaced by a rationally based approach to therapeutics steeped in molecular and clinical pharmacology, biochemistry, high energy physics, computer modeling of therapeutic strategies, and other novel disciplines. The clinical problems faced by the oncologist include overcoming the inherent or acquired resistance of the malignant cell to therapy, ameliorating the toxicities of aggressively applied therapies, and exploiting the additive or synergistic potencies of radiation, drugs, and surgery to effect optimal anticancer results. Massive cooperative clinical treatment organizations have been created to explore the potencies of these strategies when offered to large populations of cancer patients in order to provide the most rapid plausible result to the treatment community.

The problem is massive in scope and multifaceted in its presentation to the observer. Its solution is unimaginable in terms of benefit to the human condition, both in the alleviation of the pain and suffering produced by malignant disease and in the understanding of the mechanism of cellular growth and senescence.

The Malignant State: The Molecular, Cytogenetic, & Immunologic Basis of Cancer

2

Catherine A. Phillips, PhD, & Naziha F. Nuwayhid, PhD

This chapter highlights areas of research, both clinical and basic, that give insight into the causes of cancer. It considers the genetic basis of cancer at the macro level—chromosomal abnormalities—and at the micro level—molecular biology of oncogenes. It also considers the role of the immune system in tumor development and progression.

GENETIC BASIS OF CANCER

The idea that cancer has a genetic basis is supported by clinical observations that certain tumors exhibit defined familial inheritance patterns and by observations that specific chromosomal abnormalities (eg, the Philadelphia chromosome translocation in chronic myelogenous leukemia) are associated with particular tumors. Evidence that specific genetic elements or alterations are involved in tumor formation was derived from studies of animal retroviruses that cause specific cancers.

In 1911, Rous described the induction of sarcomas in chickens using cell-free filtrates. The virus identified as the etiologic agent was called Rous sarcoma virus (RSV) and was the first retrovirus to be described. Its genome was characterized, and the gene responsible for oncogenesis was designated as *src*. Subsequently, a homologous gene was identified in normal chicken cells and in most vertebrates, including humans, using a complementary DNA probe. This work suggested that the viral oncogene evolved from a normal cellular gene.

To determine whether "transforming genes" in tumors were responsible for the malignant state, a series of transfection studies were performed by Weinberg and Cooper. These investigators demonstrated that DNA extracted from human tumors and introduced into normal cells via calcium phosphate precipitation could produce a transformed/malignant phenotype in nonmalignant cells. Their results suggested that such genes were present in tumor cells. (DNA derived from about 20% of all tumors can induce transformation in some type of cultured cell lines.) Further characterization of this tumorigenic DNA has lead to the identification of altered cellular genes, mostly of the *ras* gene family. Specific oncogene families are discussed later in this section.

Mechanisms of Oncogene Activation

The mechanisms by which normal cellular genes acquire oncogenic activities are **mutation, chromosomal translocation, amplification, insertion,** and **deletion.**

A. Mutation: A cellular proto-oncogene can be converted to an oncogene via a single point mutation, causing a change of a single amino acid in the gene product. Genetic lesions of this type have been demonstrated to activate a number of the *ras* oncogenes; these single base changes result in the production of an altered p21 *ras* gene product. The normal *ras* gene product is a protein with a molecular weight of 21,000 referred to as p21. In the bladder carcinoma T24/EJ, a change from G to T in the p21 DNA coding sequence results in the incorporation of valine into the peptide chain instead of glycine at position 12. This small change is capable of changing the cell's phenotype. Chemical or environmental agents could induce transformation by generating mutations within these proto-oncogenes.

B. Chromosomal Translocation: Chromosomal rearrangements, particularly the transfer of a gene from its normal position on one chromosome to another chromosome, have been demonstrated in a number of tumors. Some translocations occur consistently in certain tumors. The consistent and specific appearance of particular rearrangements support the notion that they play a significant etiologic role in tumorigenesis. These rearrangements may lead to the activation of proto-oncogenes, as in Burkitt's lymphoma, or to the production of chimeric (fusion) proteins resulting from gene fusion, as in chronic myelogenous leukemia.

In Burkitt's lymphoma, reciprocal translocations between chromosome 8 at the c-*myc* locus and chro-

mosomes 2, 14, or 22 at or near the immunoglobulin genes occur. The translocation of a segment of chromosome 8 to chromosome 14, t(8;14), puts *c-myc* into the immunoglobulin heavy chain alpha switch region. Reciprocal translocations [t(2:8) and t(8:22)] place the c-*myc* gene together with immunoglobulin enhancer or promoter elements. Because Burkitt's lymphoma cells with this rearrangement express increased levels of the c-*myc* gene, it has been inferred that the rearrangement has influenced the regulation of this gene.

In chronic myelogenous leukemia (CML), the c-*abl* gene on chromosome 9 is translocated to chromosome 22 at the *bcr* (break point cluster) locus. This results in the production of the c-*abl-bcr* transcript and the translation into a novel tumor-specific protein.

C. Amplification: Amplification is the increase in the number of copies of a particular gene or DNA sequence. The amplification of a gene may result in the overexpression of the product encoded by this gene. Many oncogenes have been shown to be amplified and their gene products overexpressed as the result of this change in copy number. For example, N-*myc* amplification has been demonstrated in both neuroblastoma and retinoblastoma, whereas a 16-fold amplification of c-*myc* has been shown in colon carcinoma and a 20- to 30-fold amplification in the human leukemia line HL60. The prognosis for individuals with certain tumors correlates with amplification or overexpression of particular oncogenes and their products, eg, the HER-2/*neu* oncogene in breast and ovarian cancers (see below).

D. Insertion: Insertion of endogenous cellular DNA regulatory sequences, either by direct transposition or by retroviruslike integration, can result in the activation of proto-oncogenes. The integration of regulatory sequences within viral long terminal repeats (LTRs) at a position near cellular proto-oncogenes can result in their activation. The insertion of an intracisternal–A particle genome near the proto-oncogene c-*mos* has been shown in mouse plasmacytoma. The activation of the c-*mos* has been shown to be the result of reinsertion of an endogenous intracisternal–A particle genome within the c-*mos* proto-oncogene. The exact mechanism of this insertion has not been determined.

E. Deletion: Deletion may involve the loss of a whole chromosome, a chromosomal segment, or a gene. Some deletions are tumor specific while others are common to tumors of diverse cellular origins. The loss of the retinoblastoma gene on chromosome 13 and the loss of a specific region (q13) on chromosome 11 are unique to retinoblastoma and Wilms' tumor, respectively. On the other hand, loss of a specific region on chromosome 3 is observed in small-cell carcinoma of the lung, renal cell carcinoma, and ovarian carcinoma.

Deletion often results in the loss of tumor suppressor genes (also referred to as antioncogenes or recessive oncogenes), which function as negative growth regulators, ie, they regulate uncontrolled cellular proliferation by inhibiting cell division or by enhancing differentiation. Therefore, the loss of these suppressor genes or a mutation that leads to the loss of their function results in tumorigenesis. Because of their recessive behavior, the involved mutation or loss should affect both gene copies on homologous chromosomes (see below).

RB1 is a tumor suppressor gene that encodes for a nuclear protein which is involved in transcriptional regulation and control of cell division. This protein exists in phosphorylated and unphosphorylated forms. The presence of phosphorylated RB1 protein correlates with the number of cells entering DNA synthesis phase (S) of the cell cycle. Dephosphorylation of RB1 takes place during growth phase (G_1) of the cell cycle and inhibits cell division. In addition, RB1 protein is inactivated by binding to transforming proteins encoded by DNA tumor viruses such as adenovirus and human papillomaviruses.

The p53 gene is another tumor suppressor gene that encodes for a nuclear phosphoprotein with DNA binding activity. Similar to RB1 gene product, p53 also binds to several proteins encoded by DNA tumor viruses. A wide variety of tumors exhibit mutations in RB1 and p53. Transformation of cell lines occurs when the products of either of these genes are lost or rendered nonfunctional by mutation.

Viral Oncogenesis

Much of what is known about the genetic etiology of cancer is based on studies of **retroviruses** (RNA viruses). A hallmark of these viruses is the incorporation of the viral sequences into the cellular genome via the formation of a DNA intermediate that is transcribed from the RNA viral genome by the structural viral protein reverse transcriptase. The viral genome consists of three main structural genes—*gag, pol, env*—encoding for internal viral proteins, the replicative enzyme reverse transcriptase, and the envelope protein, respectively. The oncogenic potential of these viruses is independent of the replicative genes. It has been determined that the oncogenic form of the virus cannot replicate and that one of the original three genes has been replaced by a "transforming" gene.

Examples of retroviruses that are important in the etiology of human disease states are HTLVs (human T cell lymphotropic viruses) involved in the production of T cell leukemias and lymphomas (HTLV-I), hairy cell leukemia (HTLV-II), and AIDS [acquired immunodeficiency syndrome; HIV-I (human immunodeficiency virus), formerly termed HTLV-III]. Studies on these viruses and their life cycles reveal that they behave similarly to transposons (or movable genetic elements). These elements are capable of moving or "jumping" around the genome and were

discovered because of their ability to alter or modify the expression of genes by inserting into or near them.

In addition to retroviruses, **hepdnaviruses (hepatotropic DNA viruses)** and **papillomaviruses (DNA viruses)** are also capable of inserting themselves into the cellular genome and thereby altering gene expression.

Epidemiologic evidence that the hepdnavirus hepatitis B virus (HBV) is involved in the etiology of hepatocellular carcinoma (HCC) is striking. However, the molecular mechanisms that lead to HCC development are poorly understood. Data suggest that integration of the HBV into the host chromosome may lead to tumor induction either by direct activation of cellular oncogenes or by disrupting the function of tumor suppressor genes. In addition to integration, chronic inflammation and continuous regeneration of the infected liver contribute to increased mutational events and subsequent tumor development. This virus replicates through an RNA intermediate requiring reverse transcriptase and has been shown to integrate into the tumor cell genome. The hepatitis B viral DNA may be extensively rearranged and may cause chromosomal damage. DNA extracted from hepatocellular carcinomas can cause transformation in *in vitro* transfection studies. The exact mechanism of oncogenesis is unknown and probably involves more than simple integration of a viral retroelement.

Human papillomaviruses (HPV) have also been implicated as transforming viruses and have been associated with precancerous lesions and invasive cervical cancers. Additional factors may be required to produce cellular transformation. Like the hepdnaviruses, HPV 16 and HPV 18, which demonstrate high risk for malignant progression, have been shown to be integrated in the cellular genomes of invasive cancers; however, the HPV DNA is not integrated into the cellular genome in the precancerous lesions. These high-risk types are able to transform primary rat cells in cooperation with *ras* and immortalize primary human fibroblasts and keratinocytes. The transforming proteins of HPV 16 and HPV 18 bind pRB1 and p53, both of which have been shown to participate in tumor suppression. HPV-tumorigenesis is believed to be a complex multistage process. Understanding this process is important to the development of preventive, diagnostic, and curative strategies.

Temin (1989) suggested that all these viral types were derived from an ancient bacterial retron and that all these genetic elements be termed **retroelements.** This terminology suggests that the means by which the retroelements replicate and survive is related to their oncogenic potential.

Oncogenes & Their Products

Oncogenes can be classified by the relatedness of nucleic acid sequences, by the amino acid sequences of gene products, or by the enzyme activity of these products. These products may be located in the cytoplasm, nucleus, or plasma membrane, and they are similar to growth factors, growth factor receptors, protein tyrosine kinases (PTKs), or guanosine triphosphate (GTP)–binding (signal transduction) proteins. They function as regulators of DNA replication, gene transcription, GTP binding, and protein phosphorylation. Uncoupling of these activities could result in uncontrolled growth and development of tumors. Three families of these genes are described below.

A. The *ras* Gene Family: The three genes of the *ras* family are H-*ras*, K-*ras*, and N-*ras*. These genes are activated owing to a single point mutation in codons 12, 13, 59, and 61 in their p21 coding region as previously described. The H-*ras* gene is the cellular homolog of the viral oncogene found in the Harvey strain of murine sarcoma virus and has been associated with bladder, mammary, and lung carcinomas. The single base changes that are found in these tumors are at codons 12 and 61; they result in single amino acid changes from glycine to valine or aspartic acid, or from glutamine to leucine, in the peptide sequence. The amino acid change in the transforming p21 results in a more rigid molecule rather than the flexible hinge that allows the amino terminus to fold into the core of the normal p21 molecule.

Normal p21 has GTP-binding GTPase activity and an amino acid sequence homologous to signal-transducing proteins coupled to specific cell surface receptors. Mutant p21 may not be able to hydrolyze GTP (GTPase activity) and hence not be able to modulate intracellular signal transduction; the mutation in codon 12 results in loss of the ability of p21 to bind GTP. Transfection of an estrogen-dependent breast carcinoma cell line with the mutant *ras* converts it into an estrogen-independent line.

B. The C-*myc* and *myc*-like Gene Family: C-*myc* is associated with progression of cells from a resting state to a dividing state, ie, progression from G_0 to G_1 and maintenance of the potentially proliferative state. Thus, it is associated with cell growth, division, and differentiation. The c-*myc* gene product is a nuclear protein with DNA binding activity. It is activated in Burkitt's lymphoma by the chromosome translocation t(8;22) as previously described. This translocation not only activates this gene but also results in the overexpression of its product, pp62 (a phosphoprotein of MW 62,000) located in the nucleus. It has been postulated that the rate of cellular proliferation is related to the turnover rate of pp62. The increased c-*myc* expression probably contributes to the high rate of proliferation observed in these tumors.

Another member of the *myc* gene family, N-*myc*, has been shown to be amplified 75- to 500-fold in some neuroblastoma lines. This gene is homologous to the c-*myc* gene on chromosome 8 but is located on

chromosome 2. Amplification of this gene is most likely preceded by its translocation together with variable lengths of its flanking sequences. The degree of overexpression correlates with the gene copy number. C-*myc* is reported not to be expressed in tumors that express N-*myc*. In general, the greater the amplification, the shorter the time to relapse and hence the poorer the prognosis. Furthermore, it is overexpression of N-*myc* rather than simply amplification that correlates with the worst prognosis. As with c-*myc*, the N-*myc* gene product is associated with increased proliferation; proliferation of neuroblasts prevents their differentiation.

C. The HER-2/*neu* Gene: HER-2/neu (also called c-*erb* B2) was originally identified by transfecting DNA derived from chemically induced rat neuroglioblastomas into NIH/3T3 cells. It has partial sequence homology with, but can be distinguished from, the epidermal growth factor (EGF) receptor. Moreover, it has structural similarity to peptide hormone receptors, which consists of an extracellular encoding region, approximately 40% homologous to EGF receptor; a hydrophobic transmembrane domain, approximately 80% homologous to the EGF receptor; and a third (cytoplasmic) domain that contains sequences with protein tyrosine kinase activity.

This gene is amplified in 25–30% of all human primary breast tumors. Amplification and overexpression are clearly associated with stage of disease. Slamon et al (1989) assayed for gene amplification, mRNA levels, and expression of the *neu* gene product (a protein of MW 185,000; p185) in primary breast tumors by immunohistochemical staining and Western blotting. They confirmed that amplification of the gene correlates with time to relapse and survival. Overexpression is highly predictive of a poorer outcome in both node-negative and node-positive patients. It has also been shown to be associated with increased mitotic fraction. If either overexpression or amplification conclusively demonstrates an increased tumor growth fraction, then chemotherapeutic agents that are S phase–specific might be efficacious in the treatment of these cancers.

The normal HER-2/*neu* gene has been shown to induce transformation in in vitro transfection studies. Cells transformed in this way expressed the *neu* gene product at levels comparable to human breast and ovarian cancer cells. Evidence that a *neu* gene may play an etiologic role in the development of breast tumors also comes from studies in which the mutated HER-2/*neu* gene was introduced into mice. In these transgenic mice, adenocarcinomas developed in both males and females in a synchronous and polyclonal manner; no normal breast tissue could be found. This finding supports the notion that either the normal or mutant gene alone can induce the transformed state.

Data from several groups suggest that the activation of this gene results in the stimulation of the cytoplasmic receptor protein tyrosine kinase activity causing signal transduction into the cell that ultimately results in increased cell growth.

Brandt-Rauf et al have explained the mechanism by which changes in the preferred (or lower energy) three-dimensional conformation of p185 due to a single amino acid change (valine to glutamine, position 664) in the transmembrane region could cause transformation (Fig. 2–1). In the absence of p185-associated growth factor, the majority (91%) of nontransforming p185 molecules favor a three-dimensional conformation that has a "bend" in the transmembrane region which prevents receptor aggregation, signal transduction, and hence cell growth (Fig. 2–1A). In the presence of the growth factor, the normal p185 assumes an α-helical ("straight") conformation resulting in aggregation, signal transduction, and cell growth (Fig. 2–1B). The transforming mutant p185 molecules preferentially assume the "straight" conformation that permits aggregation, signal transduction, and cell growth in the absence of p185-binding growth factor, ie, growth factor–independent or autonomous cell growth (Fig. 2–1C).

How does the expression of the normal or nontransforming p185 cause transformation? A minority (9%) of the normal p185 molecules assume the higher energy or "straight" conformation of the mutant p185 (Fig. 2–1D). This small amount of the activated form of the receptor, while normally present, is insufficient to cause cell transformation. Overexpression of the normal p185 could increase the absolute number of the "straight" conformation causing autonomous cell growth. Overexpression of p185 has been described in human breast and ovarian cancers. Experimentally, 5- to 10-fold overexpression of the normal *neu* proto-oncogene causes transformation of (NIH/3T3) cells in culture, while lower levels (1- to 4-fold) do not. The conformational analyses provide a reasonable explanation for the mechanism whereby overexpression of a normal product causes cell transformation.

The use of both immunohistochemical and molecular biologic techniques for this gene and its product could be of great strategic importance in the diagnosis, treatment, and follow-up of breast and ovarian cancer.

Chromosomal Abnormalities in Cancer

Genetic rearrangement of genomic sequences is an important if not essential step in tumor development. Specific chromosomal alterations have been shown to be closely associated with various tumor types and cancer risk syndromes. For example, trisomy 21 and deletions of chromosomes 11 and 13 are associated with an increased risk of leukemia, Wilms' tumor, and retinoblastoma, respectively. The Philadelphia chromosome t(9;22) is commonly found in chronic myelogenous leukemia and the t(8;14) in Burkitt's lymphoma. (See the references at the end of this

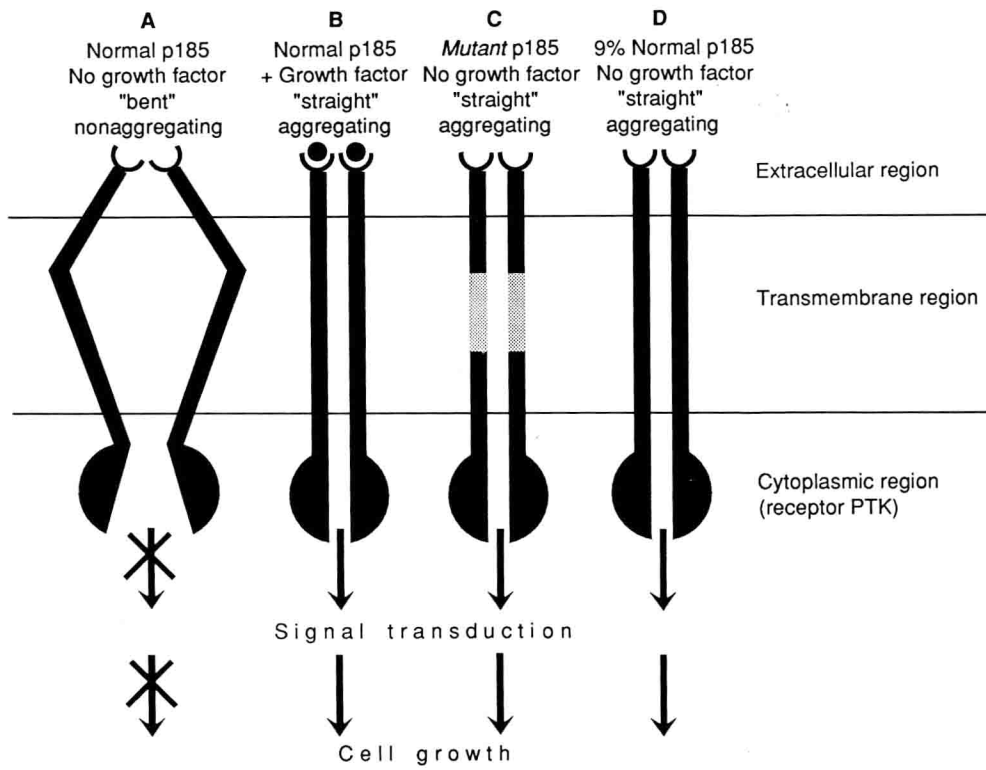

Figure 2–1. Alternative conformations of the *neu* oncogene product, p185, correlate with normal and abnormal cell growth states. ***A:*** 91% of normal (nontransforming) p185 molecules preferentially assume a conformation which has a bend in the transmembrane (TM) region that does not permit aggregation, signal transduction, and induction of cell growth. ***B:*** The interaction of normal "bent" p185 with its growth factor cause a conformational change in the TM region from "bent" to "straight" that permits aggregation, signaling, and induction of cell growth. ***C:*** Mutant (transforming) p185 molecules preferentially assume the "straight" conformation that leads to autonomous (non–growth factor–dependent) growth or transformation. ***D:*** 9% of normal p185 are found to assume the "higher energy requiring" or "straight" conformation and resemble the mutant p185 molecules in their ability to induce aggregation, signal transduction, and cell growth in the absence of growth factor. Overexpression of normal p185 causes an increase in the absolute number of the "straight" normal molecules and leads to growth factor–independent (autonomous) cell growth or neoplasia if the critical mass of receptors is attained. PTK = Protein tyrosine kinase. (Modified and redrawn, with permission, from Brandt-Rauf PW, Rackovsky S, Pincus MR: Correlation of the structure of the transmembrane domain in the *neu* oncogene–encoded p185 protein with its function. *Proc Natl Acad Sci USA* 1990;**87:**8660.)

chapter for extensive reviews and cataloging of chromosomal aberrations.)

Virtually all adult solid tumors have abnormal heterogeneous karyotypes, in contrast to pediatric tumors and leukemias that have a few clonal chromosomal defects. However, the general mechanisms that operate in chromosomal rearrangements are **translocation, inversion, amplification, partial deletion,** and **abnormal segregation of chromosomes.** The break points are often associated with oncogene loci. As discussed above, a positional change of genetic material can alter a gene's regulatory environment (eg, c-*abl-bcr* sequence in Burkitt's lymphoma). Often, inheritable tumor types show abnormal segregation of chromosomes, resulting in either monosomy or duplication of a whole chromosome complement with or without structural rearrangements. In some cases, the tumor becomes hemizygous for part of the genome because of a deletion.

In neuroblastomas, amplification of the N-*myc* oncogene is cytologically evidenced by the appearance of double minute chromosomes or by homogeneous staining regions.

In retinoblastoma, tumor cells most commonly have the chromosomal deletion 13q14 (ie, band (14) of the long arm (q) of chromosome 13 is deleted). Additional rearrangements involving chromosomes 1 and 6 also occur. In Wilms' tumor, all or portions of the chromosome region 11q13 are deleted; however, chromosome 1 abnormalities are also common. Both