CANCER GENETICS

EDITED BY

HENRY T, LYNCH, M.D.

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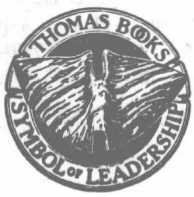

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PREFACE

THE ETIOLOGIC ROLE OF GENETICS in human cancer is enigmatic. However, significant strides toward its resolution are being made in laboratories and cancer centers in several areas of the world. Genetics is only one of many disciplines concerned with solving some of the riddles of cancer etiology and carcinogenesis. However, cancer genetics has been a controversial science, undoubtedly reflecting in part the complexity of performing genetic studies on a subject as complicated as man. For example, man's matings cannot be controlled; he has relatively few progeny; and his generation span is longer than that found in most other animal species. It is often difficult to obtain histological confirmation of cancer, especially 20 or more years after a patient's death, and yet, pathologic confirmation is mandatory for accurately assigning disease status in pedigree recording. Finally, contacting patients and informing them about the goals and objectives of the studies, particularly with respect to such an emotionally charged subject as cancer, may prove to be a formidable task; indeed psychological factors may cause an individual to cease cooperation in the very midst of an investigation. Obstacles to procuring this vital information, as well as the performing of longitudinal studies in order to learn about the natural history of the particular familial cancer problem, often plague cancer geneticists. Therefore, it is no small wonder that the greatest number of cancer genetic investigations have been performed at the infrahuman level.

This book was written primarily as an attempt to contribute order, breadth, and scope to the overall problem of cancer genetics in humans, with due consideration to the above-mentioned limitations. Thus, chapters range from basic science problems in cancer immunology, histocompatibility with particular reference to the HL-A system, oncogenic viruses, DNA problems as found in xeroderma pigmentosum, and cytogenetic problems, to more clinical-genetic-epidemiologic issues. The latter include such subjects as ethnic considerations concerned with cancer occurrence and distribution in Israel, problems in genetics, tobacco and lung cancer, genetics and specific cancers including those involving the breast, endometrium, ovary, colon, stomach, prostate, and skin, a variety of cancer syndromes, and finally a discussion of genetic counseling with implications for all of the above problems. Emphasis was given to the highlights of each of these subjects in the respective chapters. However, in the chapter by Drs. Mulcahy and Harlan, dealing with genetics, cancer, and the nervous system, an attempt was made to present this subject in a comprehensive manner emphasizing an indepth view of this entire field. This particular chapter is therefore designed to serve as the prototype for detailed coverage in a specific defined area of cancer genetics.

Emphasis has been placed upon clinical correlation of existing knowledge in the hope that the predictability of familial cancer risk might be more frequently utilized in clinical practice, i.e. for identifying patients at genetically high or low cancer risk for specific anatomic target organs in the hope of earlier diagnosis. Hopefully, genetic methodologies in due time may lead to the discovery of genetic markers which might facilitate more accurate prediction of specific cancer risks and identify patients prone to cancer sufficiently early for improved cancer control. This information should also be useful in the construction of clinical models to be utilized in the experimental design of studies of carcinogenesis.

Cancer genetics is an exceedingly broad subject, and its complete elucidation would require many volumes prepared by countless contributors. Therefore, by necessity, this book is limited in scope to selected subjects which the editor hopes will provide at least a small measure of insight into ongoing research on genetics and carcinogenesis. Concurrently, an attempt has been made to provide a frame of reference about genetic etiology in cancer for the basic scientist, the human geneticist, the clinical investigator, the practicing clinician, and the clinical oncologist.

Henry T. Lynch

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COUNTLESS INDIVIDUALS HAVE WORKED tirelessly in the preparation of this book during the past five years of its evolution. If I began mentioning these individuals by name, I would undoubtedly miss some, and this would be very painful to me. I would, therefore, prefer to express my deepest appreciation to all of you for your kindness and your generosity of time, effort, and energy.

This book could not possibly have been written without the help of many dedicated members of cancer-prone families. These patients were truly our cancer genetics and epidemiology *laboratory* from which we have gained knowledge to allow us to incorporate facts and theories into this book. The dedication of these individuals has been profound, and only those of you who have worked with families will really be able to appreciate the generosity of these dedicated subjects and the gratitude which I experience.

I am especially indebted to the several contributing authors to this book. All are individuals who have been extremely productive in their respective clinical and research disciplines and in spite of their hectic schedules, they took time out to prepare material for this book. Words cannot possibly express my personal gratitude.

Finally, I wish to acknowledge the Creighton University School of Medicine for the fine facilities, support, and whole hearted backing of this project.

H.T.L.

CONTENTS

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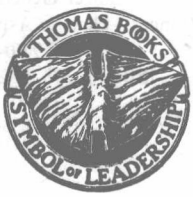

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CHAPTER 1

INTRODUCTION TO CANCER GENETICS

HENRY T. LYNCH

Historical Background

IN SPITE OF countless investigations in laboratories throughout the world, the etiology of cancer remains an enigma. Throughout the ages many different issues, events, and circumstances in the lives of men have been considered to be of etiologic significance in carcinogenesis. These conceptions have ranged from witchcraft and folklore to an indictment of physical events such as thunder and lightning, proximity to volcanoes and other major natural events and calamities. Consideration has also been given to psychological factors including fear and anxiety, man's personal habits and characteristics such as his food and dietary patterns including smoking, alcohol consumption, and other idiosyncrasies, and his familial or hereditary background including his particular race or ethnic group. Thus, when reviewing the history of cancer epidemiology in man, one finds the literature replete with "observations," many of which may or may not have been subjected to sophisticated scientific inquiry, supporting or rejecting these various hypotheses for cancer etiology [1]

For many years, physicians and scientists have considered that hereditary factors may be etiological in human cancer. However, early observations in this field were hampered significantly by two major problems: 1) lack of controlled investigations; and 2) severe limitations in the overall problem of cancer diagnosis. Nevertheless, as early as 100 A.D., a Roman physician entertained considerable curiosity about the increased occurrence of breast cancer in the family of one of his patients; however, practically no progress was made in the area of disciplined inquiry during the next 17 centuries. In 1866, Broca,[2] the renowned French surgeon, reported an increased occurrence of carcinoma of the breast in his wife's family (Fig. 1-1) which he believed must be explained on the basis of hereditary factors. In addition, he was interested in the possibility of a general cancer diathesis, since he was also struck by his observation of an increased frequency of cancer of *other* anatomic sites in this family.

Genetic and Environmental Interaction

The role of the host in the etiology of disease depends upon genetic-environment interactions. No characteristic or trait, normal or abnormal, is inherited. It is only the genetic material that is inherited; and it is this that sets the individual's range of potential reactions, i.e. the character and extent of reactions to environmental influences. At any given time, the host's constitution is the summation of his life experiences and exposures as realized within the limits of responses set by his genetic endowment. At one extreme, there are single gene alterations (mutations) that apparently impart their effects in all known genetic backgrounds and in all known environments. These are the situations to which terms such as *genetic disease* and *genetic trait* are commonly applied as a shorthand convenience. At the other

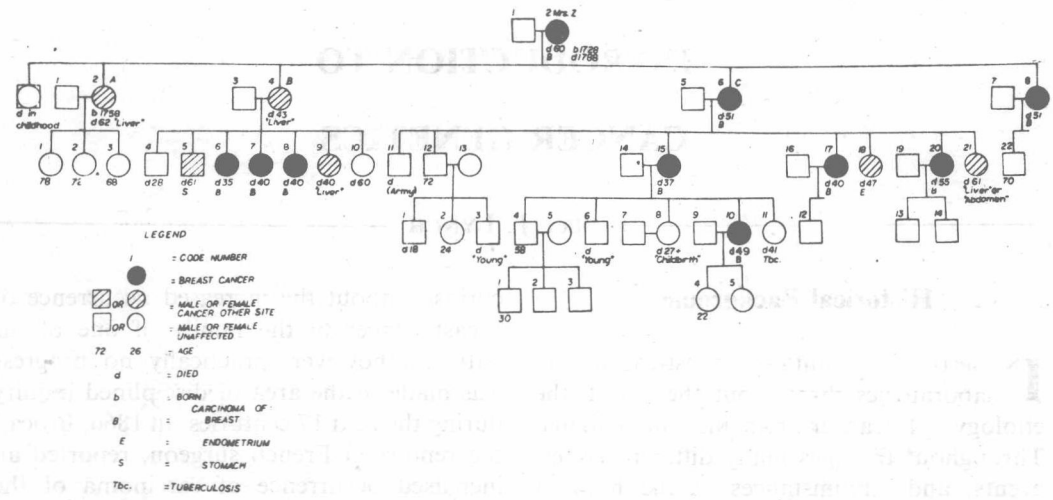

Figure 1–1. A pedigree of the family which Broca ascertained.

extreme, the effects of genotypic differences may be detectable only by statistical methods, and then, only within a limited environmental constellation. Despite the shorthand designations that geneticists may use in referring to genes and in equating gene action with specific genetic traits, many (and probably most) traits are affected by more than one gene,[3] particularly at the level of biological organization in which the majority of common disease states (such as cancer) are defined. At this level of biological organization, it is particularly important to evaluate the action of hereditary factors as strictly as possible within the context of the environments in which they are expressed.[4]

Family studies provide one of the best means for investigating genetic-environmental interactions in cancer etiology. Environmental differences may be compared between the members of high-risk families, i.e. those with remarkably high familial cancer frequencies, who have developed the disease and those who have not. The establishment of constitutional markers to identify those individuals who are particularly at risk for familial cancer may profoundly enhance the significance of such studies.[5] Different types of cancers are sometimes aggregated in the same kindred.[1] The existence of familial aggregations of these disease entities suggests the involvement of an underlying etiological unity to them.[6]

Animal Studies

As might be expected, the greatest impetus and stimulus to cancer genetic studies in man were based upon genetic investigations in laboratory animals.[7] Some of these earliest observations were based simply upon the recognition of a clustering of neoplasms in certain groups of animals as opposed to the lack of clustering in other members of the same species. Later studies revealed that cancer was not contagious in the usual usage of this term, and that certain cancers were under the influence of heredity.[1] Thus, armored with these facts, vigorous attempts were made to delineate specific hereditary tumor patterns in these animals. One of the crucial studies in this area was that of Lathrop and Loeb[7] who demonstrated that certain familial aggregations in animals manifested characteristic types of tumors and, more-

over, when certain strains were inbred, it was demonstrated that specific types of tumors were inherited as separate characters. One of the stumbling blocks which confronted these early investigators in animal cancer genetics was the heterogeneity of their animal stocks. Subsequently, homozygous strains of animals were developed for use in cancer genetic research. It was then possible to segregate particular types of tumors within these specific strains so that meaningful genetic data could be compiled and critically analyzed.

Of all laboratory animals used in these genetic studies, the common laboratory mouse has contributed most to research in cancer genetics. Its many biological and genetical advantages have been discussed at great length by Green and his staff at the Jackson Laboratory at Bar Harbor, Maine.[8] Indeed, mice have been used extensively for cancer research ever since C. C. Little established the DBA strain in 1909. Many genetic hypotheses have been tested through the years such as the relationship of disease incidence among different mouse strains and the evaluation of host factors and exogenous factors. Selective inbreeding studies with careful evaluation of new mutations in these animals have subsequently contributed to the comprehension of the etiology of a variety of diseases including cancer in man.

More than 70 strains of homozygous mice are now available for study by cancer geneticists, some of which include: 1) strain BALB/C which developed a high incidence of pulmonary tumors and lymphatic leukemia; 2) strain C57 Black, a tumor resistant strain in which few mammary or pulmonary tumors develop; and 3) strain C3H in which a high incidence of mammary tumors and hepatomas occurs.[8]

Studies of cancer genetics at the infrahuman level have had the advantage of controlled experimentation, the lack of which is obvious and of course poses a serious deterrent in human studies. Thus, the development of highly inbred strains of animals has made it possible to evaluate the genotype of the host with a high degree of precision. In turn, the role of environment and its interactions with the genotype has made it possible to evaluate the exigencies of this interplay with a high degree of accuracy. Thus, in certain well designed animal experiments, it is possible to draw conclusions for a genetic hypothesis for cancer etiology; namely, we can evaluate the relative roles of genetics and environment in carcinogenesis. The general conclusion stemming from numerous studies of this nature, i.e. wherein genetic and extra-genetic factors can be controlled, has been that the individual's genotype plays a major role in response to carcinogens; thus, it is obviously mandatory that carcinogenic factors be evaluated critically in their relationship and/or interaction with host factors. However, one must realize at the outset that an all-or-none law as a frame of reference in terms of quantifying genetic and environmental carcinogenic factors is not possible when interpreting animal data, and in the case of humans, the problem is considerably more complex. For example, leukemia can be produced invariably in certain animals and in man through massive doses of radiation. Similarly, an excess of chemical carcinogens such as methylcholanthrene, urethane, and nitrogen mustard will invariably induce cancer in animals and probably in man. However, when such a massive exposure to carcinogens is administered, the investigator is hampered in his understanding of the role of host factors since these are literally overwhelmed by the massive carcinogenic dose. Contrariwise, certain animal strains can be highly inbred so that they manifest an exquisite genetic susceptibility to cancer; in this case it becomes difficult if not impossible to evaluate the relative importance of nongenetic factors. Thus, in some of the simple Mendelian inherited

precancerous syndromes in man such as the multiple nevoid basal cell carcinoma syndrome and familial polyposis coli, the genetic "carcinogenic" component may be so strong that it is difficult to study the possible interacting role of environmental factors in cancer etiology.[1]

The above considerations notwithstanding, Heston[9] generalized that every variety of neoplasm, regardless of the species in which it is manifested, is probably to some degree under the influence of genes. Thus, he viewed genetic factors as crucially important even when nongenetic factors such as an oncogenic virus is known to be involved. He stated, for example,

> When an oncogenic virus is involved, the genotype of the host may control the propagation and transmission of the virus or the malignant response of the cell to the virus. When a chemical or physical carcinogen is introduced, the genotype of the organism may control the malignant response of the cell to the carcinogen and determine in which tissue or tissues this response will occur. But the importance of the genotype may be most clearly shown in the occurrence of the so-called spontaneous tumors—those with which no external biologic, physical, or chemical carcinogen has been identified.

Successful genetic investigations have been made using specific strains of these laboratory mice in which susceptibility to certain malignant neoplasms has been developed, characterized and now catalogued. These include strains which have been bred for susceptibility to practically every histologic variety of cancer including leukemias, mammary tumors, lung tumors, osteogenic sarcomas, and a variety of carcinomas. Other laboratory animals of different species, including the rat and chicken, have also been bred for susceptibility to specific malignant neoplasms. However, in spite of the relative ease in producing and maintaining inbred strains of laboratory animals for susceptibility to specific malignant neoplasms, the genetic mechanism in many cases appears to be complex. For example, in mice, Heston[9] stated that of all the types of tumors for which evidence of genetic influence has been found, not one example has been observed to be due to a *single* gene. Rather, these tumors appear to be inherited in terms of threshold characters[10] or so-called quasi-continuous characters as suggested by Grüneberg[11] and used interchangeably with the threshold concept by Heston.[9] This term signifies that these tumors can be influenced by a multitude of genetic and extra-genetic factors. However, alternative expression may occur because of differences in thresholds for development of cancer. In addition, this term does not imply that the characters are necessarily found in all or none of the individuals of a particular inbred strain, but rather that they occur in certain incidences characteristic of the particular strain. Finally, Heston[9] stated that when the strain is inbred to fix the genotype, the genotype will then establish the incidence of the specific malignant neoplasm. In turn, a variety of extra-genetic factors will interact with this specific genotype and this specific interaction will then determine the expression of the development of the tumor. This line of reasoning is supported by abundant laboratory experiments at the infra-human level and it certainly has many implications for the study of cancer genetics in man.

The concept of threshold character in cancer epidemiology is perhaps best seen in the case of mammary tumors in the mouse. In this particular tumor, the role of genetic factors has been firmly established; it is known that specific genes on specific chromosomes can materially alter the incidence as well as the average age for the occurrence of this tumor. However, in addition to the

role of specific genes in the etiology of this tumor, it is just as firmly established that a mammary tumor virus as well as other factors including chemical carcinogens, radiation, endogenous hormonal stimulation, and administered estrogens play a critical role in its production. When the majority of these influences are present, we can expect a high tumor response by altering these factors.

In context with threshold factors and the inherited susceptibility of cancer, single genes may have an exceedingly potent effect on the incidence of certain tumors. This is seen clearly in the case of ovarian tumors which may be increased from virutally 0 percent to 100 percent by the dominant spotting gene.[12] However, we must realize that spontaneous ovarian tumors may still occur in the absence of this particular gene and that incidence may be influenced by the presence of other genes. Furthermore, such factors as radiation may also influence the expression of this tumor.

While several cancer and precancerous diseases in man appear to be under the control of a single gene, simple inheritance of cancer in laboratory animals has been encountered infrequently. One example involves renal adenoma in the rat as described by Eker and Mossige.[13] However, as in experimental animals, the majority of tumors in man that appear to be under hereditary control do not show simple inheritance; rather they appear to be due to complex genetic mechanisms, involving multiple genes in interaction with a variety of environmental factors. In these cases, the risk for cancer to close blood relatives of the cancer proband may be given in statistical terms by so-called empirical risk figures; these risk estimates by themselves do not provide firm knowledge of the true significance of genetic and/or extra-genetic factors. In short, they do not necessarily shed light on cause-effect relationships in carcinogenesis. While the complex nature of inheritance of cancer in man poses a challenge to the ingenuity of cancer epidemiologists, obviously it leaves the door wide open for scrutiny of how genotypic factors in association with extra genetic factors, i.e. biological and chemical carcinogens, operate dynamically in the production of cancer.

An example of the importance of threshold concepts of inheritance of cancer in animals, with implications for man, is seen in pulmonary tumors. The relationship between genes and chemical carcinogens in pulmonary tumors in the mouse, has been studied in depth. The rate of spontaneous pulmonary tumors in specific inbred strains of mice increases through chemical induction by methylcholanthrene, dibenzanthracene, urethane, and nitrogen mustard, but the strains nevertheless retain their relative rate of incidence of spontaneous pulmonary tumors.[14,15] Interesting parallels are found in humans as evidenced by the work of Tokuhata and Lilienfeld.[16] Specifically, cigarette smoking has caused an increase in pulmonary cancer in almost epidemic proportions, and has permitted studies of the genetics of this disease in concert with the role of inhaled carcinogens. A genetic component has been determined which appears to be more potent among nonsmokers than among smokers; however, there appears to be a synergistic interaction between host factors and inhaled carcinogens much in keeping with the models established in experimental animals.[16] Thus, from this particular example, we see clearly that in studying the epidemiology of tumors in man, we must weigh carefully the relative importance of both genetic and nongenetic factors.

The role of viral factors in the etiology of cancer in man is of utmost interest. Nevertheless we must not lose sight of the fact that genetic factors may also be of critical importance in these problems. Thus, there are many examples of host specificity in tumor viruses. For example, mammary tumor virus