The Chromosomes in Human Cancer and Leukemia

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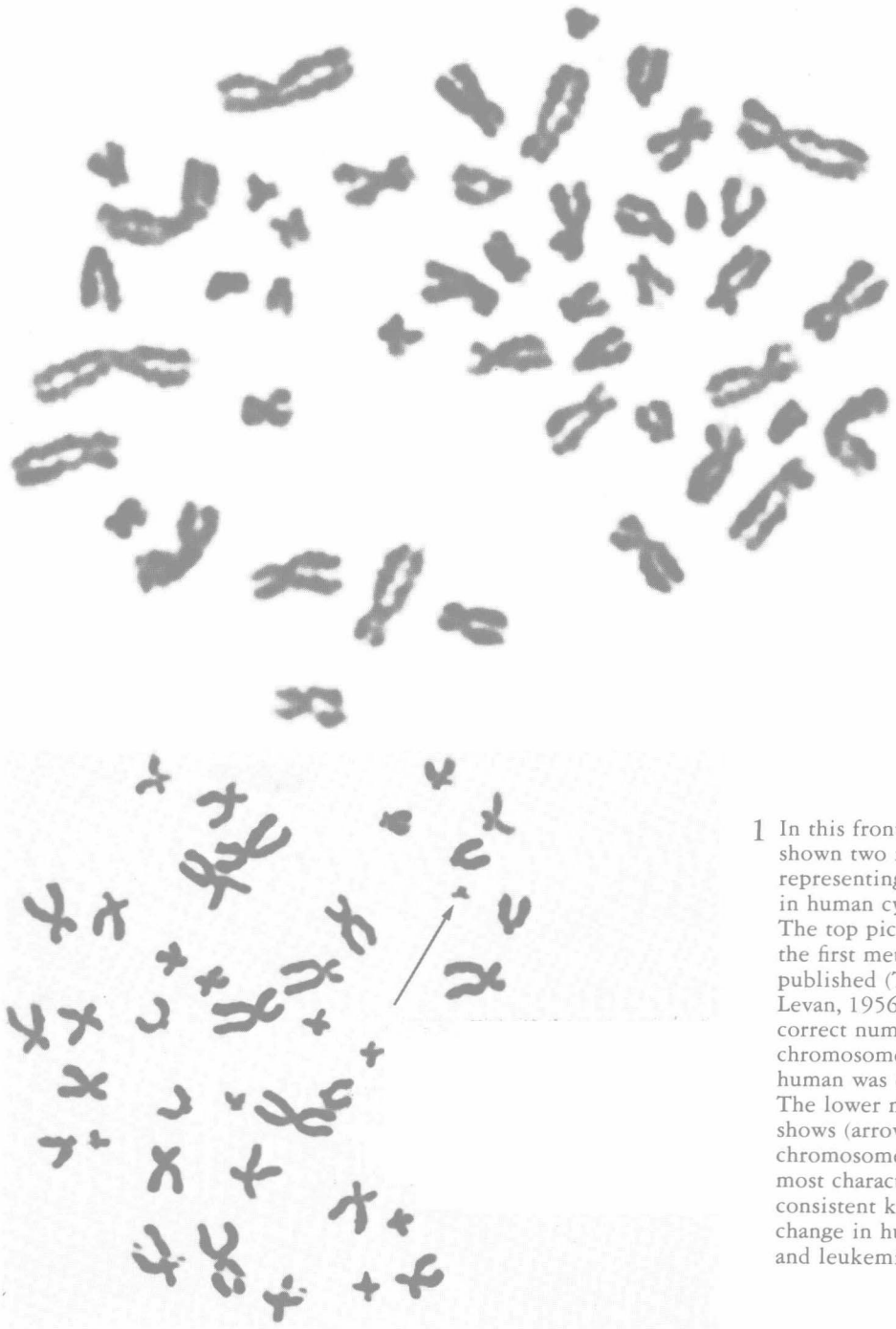

1 In this frontispiece are shown two metaphases representing milestones in human cytogenetics. The top picture shows the first metaphase published (Tjio and Levan, 1956) in which the correct number of chromosomes in the human was established. The lower metaphase shows (arrow) a Ph^1-chromosome, to date the most characteristic and consistent karyotypic change in human cancer and leukemia.

To my wife, Maryn,
without whom nothing would have been possible

Foreword

Cancer is a malignant form of uncontrollable cellular growth occurring in an organism through a continuous series of cell generations. Both the origin of malignant development and its management require a full understanding of cytological principles based on the use of a variety of methods, as abnormal growth and its inhibition are intimately connected with the mechanisms of cell division. About 100 years ago, microscopic studies of cancer in domestic animals were undertaken; however, because of technical limitations at that time, gross histological aspects were primarily presented. Not long thereafter emphasis was given to cytogenetic studies of malignant material, since cancer originates from pre-existing somatic cells, and cellular phenomena involving various mitotic events must have an essential bearing upon the prime elements of many cancer problems. The genetic constitution of individual cancer cells reflects the genetic pattern of the tumor; it is these individual cells that maintain a distinct genetic pattern for each tumor and determine its genetic nature. Thus, successful investigations of the genetic nature of cellular changes in tumors, as represented by the chromosome constitution, are important in solving the mechanism of malignant transformation.

Much interest has been generated by the many types of chromosome changes observed in almost all cases of cancer studied to date. Theodor Boveri advanced the theory that mutation in the genetic constitution of cells, particularly in the chromosomes, may explain the change from normal to malignant status.

Until relatively recently, the data on the chromosome constitution of cancer were utterly confused. Much of the older literature merely described high mitotic rates, a remarkable frequency of mitotic abnormalities, and striking aberrations of chromosome numbers as universal features of neoplastic cells. Extensive studies of transplantable tumors in rodents subsequently revealed that specific cells have a characteristic chromosome constitution contributing to the growth and development of the tumor in a new host, generating a stemline lineage. Following these studies of animal tumors, and based on them, much critical information was gathered regarding the significance of chromosomal mechanisms in malignant transformation. Furthermore, current

advances in the technical methods in the field of mammalian cytogenetics have afforded a precise and reliable analysis of the chromosomes in the cells of mammals, including man, *in vivo* and *in vitro.* These methodologies have provided karyological data essential for the understanding of some of the etiological aspects of various types of diseases and established the importance of chromosomal data in cancer as helpful criteria for clinical and pathological considerations, and in the understanding of the mechanisms of malignant growth. The cytogenetic findings in human tumors have been shown to be comparable in many ways to those obtained in experimental and spontaneous tumors in animals; however, valuable information, supplementing the knowledge gained through animal studies, has been provided through the acquisition of karyotypic data in human neoplastic cells. Furthermore, the introduction of modern cytogenetic techniques, and the subsequent discovery of the association of many syndromes with specific types of abnormal karyotypes have led to this field becoming one of considerable clinical importance.

Dr. Avery A. Sandberg, the author of this book, has long been involved in cytogenetics, as a leading investigator in the field of human neoplasia as well as of congenital disorders. "The Chromosomes in Human Cancer and Leukemia", based on his experience, consists of some 850 pages and contains over 200 figures, more than 100 tables, and nearly 4,000 references. The book presents the chromosome findings in various cancerous conditions of man and a detailed, inclusive overview of many major areas of chromosome findings, both clinical and investigative, of human neoplasia, with emphasis on the contribution of these findings to a better understanding of the pathology and clinical aspects of human cancer and leukemia. To a large extent, the volume is a chronicle of his own detailed work, made through joint efforts with his colleagues and well-trained students, all providing an enormous amount of information in the relevant fields mentioned above. It reflects the ebullient energy of Dr. Sandberg.

This book contains a well-organized presentation in the following areas: chromosome breakage syndromes, lymphomas, plasma cell disorders, primary and metastatic cancer, cancers of specific sites such as those of the alimentary tract, female organs, urinary tracts, male organs, lung, thyroid and adrenal, melanoma, brain and nervous system, and so on. Details of many of the methodologies used in cancer cytogenetics, as well as those in congenital disorders, and the effects of noxious agents and viruses are presented in a well-arranged fashion. These elements give the book a special value as a reference volume. In addition, the newly developed chromosome banding procedures, each useful in the characterization and identification of normal and abnormal chromosomes, as well as a large body of data of new and significant findings derived from their application, are presented. Synoptic views of specific chromosome changes in human cancer and leukemia, together with the historical background, and the citing of the most essential publications, constitute an impressive and outstanding presentation and a ready source of cancer cytogenetic material for the reader. All these facets will be advantageous to a great extent not only to scientists in clinical and medical fields, but also to those in a variety of disciplines such as biochemistry, molecular biology, evolutionary genetics, and practitioners, as well as for lay persons.

In my opinion, the publication of this book reflects the vast knowledge in the fields of both human oncology and cytogenetics and bears witness to the vast production and devotion of workers involved in this intellectual discipline and scientific endeavor.

Over the years, I have come to be associated with Dr. Sandberg, both through our chromosome research work, as well as through the collaboration of many of my students, who have worked with him in Buffalo. It is a pleasure and an honor to have this opportunity to express my appreciation for his outstanding contribution to the science of cancer biology and cytogenetics.

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Preface

The evolution of my interest in cytogenetics may be worthy of record, because not only is my work in steroid metabolism often assumed to be that of another individual, but, in fact, this work was responsible for leading me into the field of cytogenetics. In the late 1950s we were engaged in studying testosterone synthesis by testes of subjects with Klinefelter's syndrome and other forms of gonadal dysgenesis or disease. To ensure the nature of the abnormalities affecting the testes being utilized in our studies, I committed myself to the establishment of a cytogenetic laboratory in my department, necessitating a period of intense study and training in the field. In addition, the then existing needs of the medical community and the various hospitals led to an expansion of my cytogenetic laboratory, and the subsequent study of chromosomes in human cancer and leukemia. Roswell Park Memorial Institute was an ideal place for the study of the latter disease, because not only is it a recognized center for the treatment of cancer and leukemia, but also its staff is deeply committed to understand as much as possible about these diseases. Thus, it is not surprising that over the years I have enjoyed the utmost cooperation from the clinicians and surgeons of the various services at Roswell Park Memorial Institute. In addition, I have been fortunate to have had associates, many of them from Japan, who have contributed to the field of cytogenetics, and in so doing have enlarged my knowledge of and appreciation for the chromosomal changes in human disease. To all of these individuals I offer my sincere thanks and gratefulness.

Even though a large number of references are given in this book, the list is not all inclusive. I have included only references to papers I had the opportunity to read, excluded some which duplicated papers of authors published in more than one journal but did not contain any additional information, and obviously could not include those papers of which I was not cognizant or had been unable to obtain for reading.

I wish to thank my secretarial staff, in particular Mrs. Cathy Russin, for taking care of the various clerical aspects of the book; a number of authors who have kindly supplied

me with manuscripts and data prior to publication and/or pictorial material for use in this book; the Departments of Medical Illustrations and Medical Photography for their help in so many different ways; and Dr. Surabhi Kakati of my department for her help in writing several of the chapters.

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Introduction

The description of an impressive number of human developmental disorders and diseases associated with *gross* chromosomal changes during the 20 years since the establishment of the correct number of chromosomes in man represents an epochal period in medicine and genetics. The field of cytogenetics, including human cytogenetics, has become an established discipline in its own right, as evidenced not only by the appearance of an array of journals and books dealing with this area, but also by the fact that the material published has been beyond the scientific appetite or comprehension of any one individual. Hence, it is the major aim of this book to focus almost exclusively on the correlation of karyotypic changes with specific human cancers and leukemias. Even this limited approach to human cytogenetics may be too much for one individual to accomplish, but it is the only way in which my views, opinions, and, possibly, prejudices in this field can be presented unabashedly, clearly, and, I hope, responsibly, and within the context of a critical and comprehensive correlation and summation of chromosomal changes with every malignant disease described to date.

Developments in the area of cytogenetics have overlapped with those on the molecular basis of genetics, i.e., the structure and function of DNA, and the architectural scheme of chromosomes in relation to the newly acquired knowledge of DNA.

This book will concern itself with *visibly recognizable* chromosomal changes in human cancer and leukemia. Thus, until recently, these changes consisted exclusively of readily ascertained morphologic and/or numerical changes of the chromosomes involving, in genetic terms, very large amounts of DNA. Newer techniques of fluorescent staining and banding patterns of chromosomes have already revealed finer karyotypic features in cancer and leukemia, too delicate to have been realized with the older methods. No available method, however, is capable of visibly showing changes at the gene level. Inasmuch as such a change is probably an essential part of carcinogenesis and leukemogenesis, our inability to examine chromosomes at that level will continue to be an egregious shortcoming of oncologic cytogenetics. Thus, even though

emphasis has been put in the following chapters on *gross* (visibily recognizable) changes as seen with microscopy, including electron microscopy, it must be remembered that until we have means of reliably recognizing functional or molecular changes at the gene level, which may be the most common, if not sole, site of genetic changes (mutations) resulting in cancer or leukemia, our understanding of the causation and role of chromosomal changes in these conditions will continue to be incomplete.

The chromosomal alterations in human cancer and leukemia are almost always confined to the cells of the neoplastic tissues. For example, the chromosomal changes in acute leukemia are present only in the leukemic cells of the marrow or blood; those in various cancers are present only in the involved tissue and are not reflected in the karyotypes of the blood lymphocytes of cultured skin cells, which almost always reveal a diploid pattern. Thus, the karyotypic picture of the cancerous and leukemic cells is of value to clinicians, biologists, cytogeneticists, pathologists, and researchers interested in cancer and leukemia.

In this book an attempt has been made to present a comprehensive evaluation of the cytogenetic findings in human cancer and leukemia, with emphasis on those areas pertinent to medical oncology and pathology; and, additionally, on those areas not covered in previous reviews and books. In a number of cases the author presents his personal views, views, as often happens, that may appear putatively erroneous as evidence is obtained with new methodologies or approaches. In these, he has drawn generally on his own experience, though he has relied heavily on those publications that contain comprehensive and sufficient information for reliable interpretation. However, the guiding principle in and the special emphasis of this book will be a correlation of specific diseases and their subdivisions with their chromosomal picture, so that, busy clinicians, medical students, and clinical and basic science researchers will not need to search the widely dispersed and voluminous literature for their data.

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