Diagnosis and Treatment of

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Introduction

During the past several decades great strides have been made in the fundamental knowledge of medical sciences. In no other field has greater progress been made than in diseases of the chest. It has become inevitable that studies relating to these conditions should become more or less specialized, depending on organs affected and types of disease. Thus, such diseases may be presented anatomically, e.g., those of the tracheobronchial tree, pulmonary parenchyma, pleura, diaphragm, esophagus, mediastinum, cardiovascular system, etc.; or etiologically, e.g., inflammations, bacterial, viral, mycotic, parasitic, collagen diseases, diseases of industrial and congenital origin, and tumors, etc. The need for a detailed description and presentation of etiologic factors and recent proven methods of treatment in particular fields of thoracic diseases requires space impossible to include in one cover to cover volume. It seems wise that the authors should choose to report investigations and treatment of particular disease groups separately. Dr. Spain, who has had a wide clinical, laboratory and pathologic experience has wisely chosen to bring you, through his own observation and those of his distinguished coauthors, the soundest present day thoughts and observations on tumors of and within the thorax. Pathogenesis, structural details, complications, diagnostic armamentaria and therapeutic measures including the use of antibiotics, radioactive substances and surgical measures, have been handled in the greatest possible detail without leaving much "chaff with the wheat." The specialized experience of the various authors assures the reader a comprehensive and informative guide to the better understanding of the various tumors and their more efficient treatment.

Since its organization twenty-five years ago, The American College of Chest Physicians has encouraged and sponsored the education of the physician in the field of diseases of the chest. The College is proud to sponsor and recommend this fine volume, *Diagnosis and Treatment of Tumors of the Chest*, because of the excellent content therein and because it recognizes the present day need for detailed reporting of the various groups of abnormal entities. This volume should prove useful not only as a text for specialists in thoracic disease, but also as an excellent reference work for undergraduate students and practitioners having a particular interest in fields closely related to diseases of the chest. It should also be valuable to workers interested in the clinical and research aspects of tumors in general.

Donald R. McKay

Preface

Any text attempting to deal with the subject of neoplasms, even on the most practical clinical level, must do so within the frame of reference of the present state of our knowledge in the field of experimental and basic cancer research. At present there are many conflicting theories as to the etiology of the various forms of cancer. These include the well known virus concept, immunologic mechanisms, somatic mutations, and chemical and endocrine carcinogenesis. Despite the establishment of viruses as etiologic agents in many animal tumors, in only one human neoplasm (the skin wart) has a virus etiology been established at present. Currently, our basic knowledge of cancer consists of the following established facts. (All else remains controversial, speculative and unproven.) Neoplasia consists of cells which proliferate with no restraint, in contrast to the normal growth of cells which is limited. Growth of the tumor may be related to changes in the host or to changes within the tumor cell itself. The former tumors are called dependent and the latter autonomous. Within the host, tumor growth may be altered by sustained excessive stimulation or a deficiency of natural restraining forces. Within the tumor itself, the rate of growth may be cytogenic or outside of the self-replicating apparatus of the cell. Some autonomous tumors respond to physical regulating mechanisms. Others do not. The general trend in malignant neoplasia is for progression, i.e., from bad to worse, from a good response to a poor response and from normal function to nonfunction. The differences between benign and malignant are poorly understood and it is unclear whether these should be grouped together as similar disease processes. Clearly, from the foregoing information there is nothing that can be of immediate practical help to the clinician in the definitive therapy of the patient with carcinoma. Despite recent advances in the synthesis of anticancer chemicals and further insight into antimetabolites and enzymatic behavior of cancer cells, chemotherapy at present only offers temporary relief in a limited number of instances. The clinician today must rely on the tried and tested procedures of early and accurate diagnosis and judicious surgical and radiation therapy. Early diagnosis today is helped by the improvement in our radiographic technics and the addition of various biopsy methods and exfoliative cytology. Treatment has benefited by better understanding of electrolytes, improved anesthesia and refined surgical procedures. Radiation therapy can be delivered in higher doses to more concentrated areas. It is hoped, but as yet unproven, that mass radiography and mass cytologic studies may provide the means for earlier diagnosis and a higher cure rate.

As yet, none of the results from any particular method of treatment have

been subjected to rigid biostatistical evaluation. For this reason, in addition to some overlapping of material in various chapters, one must also expect reasonable differences of opinion as to the best treatment for any particular type of tumor.

An eminent leader in the field of cancer research has recently stated that it may well be that some simple practical methods, not necessarily related to the basic aspects of cancer growth, may bring a solution to the practical aspects of cancer control. When this comes about, research into the basic mechanisms that produce cancer will rightly be regarded, partially at least, as an intellectual exercise. In this sense, the important discovery, to which this book devotes considerable space that cigarette smoking is a major cause of bronchogenic carcinoma, provides a means for eliminating the major portion of this form of cancer. It is hoped that the material in this text will provide sufficient moral and scientific ammunition for the practicing chest clinician to devote sufficient time to the prevention of this form of cancer. If and when this comes about, further studies on the biologic nature of bronchogenic cancer which are as yet not understood, will truly be in part an intellectual exercise.

The title of this book is *Diagnosis and Treatment of Tumors of the Chest*. It is hoped that a revised edition or an entirely new book on the subject will eventually be entitled *Prevention, Diagnosis and Treatment of Tumors of the Chest*.

The presentation of the material in this book is dedicated to the concept that research, education and patient care are the continuing, interrelated keystones on which the modern practice of medicine is based.

David M. Spain, M.D.

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Contents

CHAPTER 1

On The Etiology of Bronchogenic Carcinoma

By MICHAEL B. SHIMKIN, M.D.

PRIMARY PULMONARY CARCINOMA HAS BEEN RECOGNIZED for well over a hundred years. Descriptions of cases are to be found with increasing frequency in the medical writings of the nineteenth century. In 1879, Härting and Hesse established that lung cancer accounted for a high proportion of pulmonary deaths that were the scourge of the Schneeberg miners, the first example of environmentally induced lung cancer.

Primary carcinoma of the lung, as all other major forms of neoplastic disease, has been described to occur in all human populations and many animal species that have been adequately studied. It has become increasingly more convincing from recent investigations that carcinoma of the lung represents a group of separable diseases. The epidermoid and anaplastic morphologic types of bronchogenic carcinoma in man are associated with known environmental factors, occur more frequently in males than in females, and have shown an increase in incidence throughout the western world (Dunn, Doll). In contrast, adenocarcinoma of the lung appears to be much less related to known environmental factors, is more evenly distributed among males and females and has been relatively stable in incidence (Kreyberg). The bronchiolar carcinoma appears to be still another neoplastic entity, morphologically resembling the primary adenomatous tumor of the mouse and the infectious adenomatosis of sheep.

Primary pulmonary tumors in animals are usually of the adenomatous type, and the distribution by sex is approximately equal. The lung tumor of the mouse has been studied extensively, and similar tumors are found spontaneously and can be induced with carcinogens in the rat and guinea pig. Bronchogenic carcinoma resembling the human tumor has been induced in rats following exposure to radioactive inhalants (Cember and Watson).

Among domestic animals, pulmonary neoplasms have been described most frequently in dogs and in horses, probably because these species are permitted to live to older ages. Individual case reports of lung cancer include wild animals in zoologic parks, such as a jaguar, a kangaroo and a civet. There is also one report of an adenocarcinoma of the lung in a fowl (Shimkin, Steiner).

These general comparative descriptions lead to the following generalizations: (1) Lung cancer was known before industrialization was well advanced and before cigarettes existed; (2) the basic causes of lung cancer

are widely distributed among human and animal populations; (3) there are several neoplastic disease entities with diverse etiologies grouped under the anatomic designation of lung cancer; and (4) environmental inhalants can lead to the induction of lung cancer in man and in laboratory animals.

The Increase in Bronchogenic Carcinoma

About 30 years ago it began to be suspected that primary pulmonary cancer was being encountered more frequently. The early impressions were based usually on autopsy series in which lung cancer became increasingly more prominent relative to other causes of death or other types of neoplasms. It is primarily in retrospect that this rise in incidence was noted in the national vital statistics of the United States, Great Britain and other western European countries (Dunn). In the United States, even retrospective analysis of such statistics encounters the difficulties of interpreting changes in classification, incomplete coverage, and the inadequate evidence on which many of the early reports on neoplastic diseases are based (Milmore). For these reasons, the increase in lung cancer was a matter of serious debate, and it is only during the past decade that it has become clear that pulmonary cancer is a phenomenon that can be described as a neoplastic pandemic (figs. 1 and 2). And the incidence rates for successively younger cohorts continue to rise (fig. 3).

From a rare disease of 50 years ago, lung cancer has climbed to the first position of site-specific neoplastic deaths among men. In the vital statistics of the United States for 1956 it accounted for 29,000 deaths of which 25,000 were among males. In men over 50 years of age, more deaths are attributed to lung cancer than to all other respiratory diseases. The recorded mortality is even higher in some western European countries and in Great Britain (Doll). Correction of crude mortality rates to relate them to a standard population of a fixed age distribution does not affect the trend of the rates

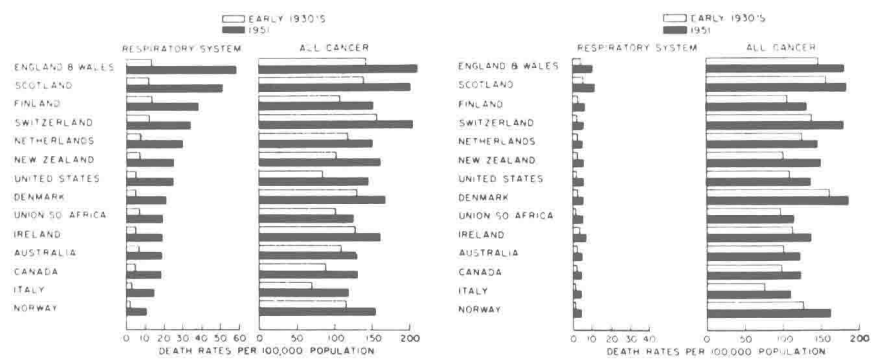

Fig. 1—Crude mortality rate for cancer in selected countries; (*left*) men; (*right*) women (from Dunn).

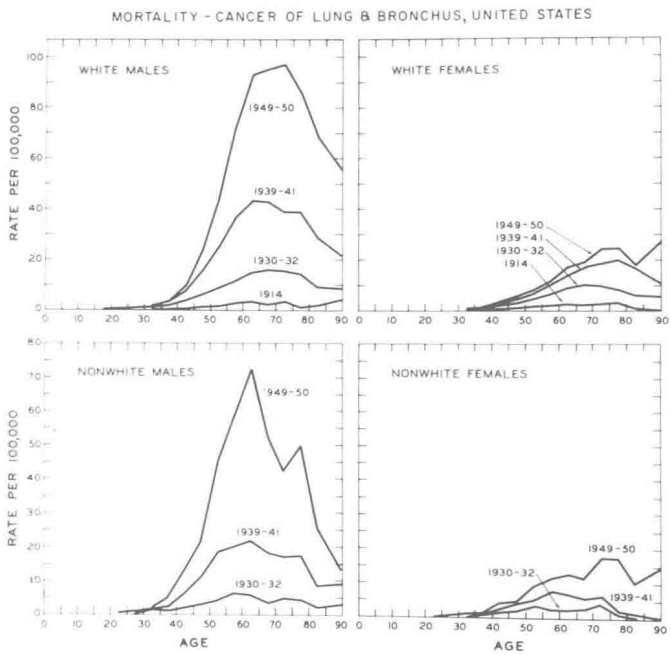

Fig. 2—Death rates for cancer of the lung in the United States, selected years 1914–1950, classified by age, sex and race (from Dorn and Cutler).

appreciably, indicating that the aging of the population is not a prominent feature in this increase (Dunn).

Primary pulmonary cancer is not an easy disease to diagnose, and in many early autopsy series the correct clinical diagnosis was missed in more than 90 per cent of the cases. The past 50 years have seen the introduction of the roentgenogram and the fluoroscope, the bronchoscope and thoracotomy; tuberculosis and other respiratory diseases have decreased as causes of death, and antibiotics have unmasked neoplasms that were previously obscured by pneumonia; hospital records and vital statistics have improved. What, then, is the basis for believing that lung cancer has truly increased, rather than that the figures merely reflect better recognition and reporting, and other statistical artifacts?

This particular question, and its various ramifications, has been the subject of many astute analyses, conferences and international symposia. The following are among the many facts that support the thesis of a real increase in lung cancer and, conversely, that are inconsistent with the explanation of spurious statistics for the major proportion of the increase:

1. The increase in death rates from lung cancer continues, and is just as evident now as 20 years ago. During this time there has been no other neoplastic site or type that has manifested a comparable increase.

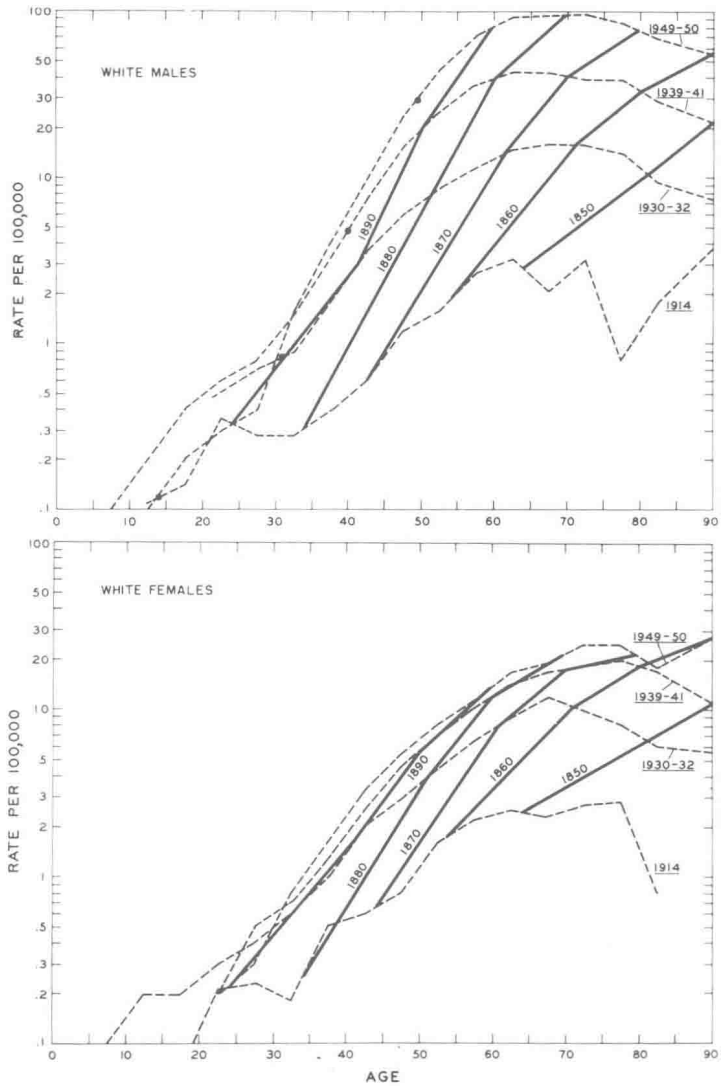

Fig. 3—Death rates for cancer of the lung for white males (*top*) and white females (*bottom*), by age, United States, selected 1914–1950, arranged to show cohort rates (from Dorn and Cutler).

2. The increase is more marked for males than for females, and this disproportion has become greater during the more recent years. It is unlikely that greater diagnostic acumen, or better recording, is exercised for men than for women.

3. The increase has been approximately the same among physicians in the United States and in Great Britain as among the general population of the two countries. Presumably physicians have better access to and use of diagnostic technics than the general population.

4. The increase has been most marked for epidermoid and anaplastic carcinoma of the lung, while adenocarcinoma has remained relatively stable.