WILLIAM A. CREASEY

CANCER

AN INTRODUCTION

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This book is dedicated to those patients with whom the author worked, who so willingly gave of themselves to help advance our understanding of cancer and its eventual conquest

Preface

At this time, there is a very intense interest in cancer, a fact reflected in the vast public funding programs for cancer research. This research extends over the whole spectrum of biology, in addition to the traditional medical specialties, and thus involves scientists from a wide range of disciplines. In view of both the public interest, and the variety of disciplines being mobilized for cancer control, it is important that the opportunity to learn about the disease should be available to all. For the most part, the available books on the subject, as would be expected, are either comprehensive volumes aimed at a readership already well versed in medicine or specialized texts dealing with specific areas of medicine or cancer research. There is clearly a need for a broad treatment that has less emphasis on pathology, diagnostic techniques, or details of therapy and more emphasis on cancer biology and trends in research than the traditional medical texts.

While teaching the principles of cancer biology and pharmacology to undergraduate and graduate students, I was made acutely aware of the lack of a suitable introductory text for such students, as well as for non-medical research workers. Medical students would also find such a text useful as a basis for their later, more intensive clinical studies. This book is intended to serve such a need. I have endeavored to bring together in one volume a range of materials on the nature and incidence of cancer, the features of cancer growth and metastasis, the biological interactions between the tumor and the host, the principles of diagnostic approaches, the various fac-

tors known or suspected to produce cancer, the forms of treatment, and some of the major directions in cancer research. I have not dealt exhaustively with either the molecular biology of cancer or its clinical aspects; others are better qualified to do this.

I realize that to some extent personal attitudes have determined which topics should be included and which omitted. In this I am reminded of a review of the late Sir Winston Churchill's *History of the English Speaking People*, in which the critic wrote that a more appropriate title would have been *Things that Interest Me in History*. Many, for example, might object to the amount of space given to psychological aspects of cancer etiology, or to an analysis of unproven remedies, but my own feeling is that information on these topics is hard to come by, and its presentation may encourage more definitive studies, whereas the molecular biology of cancer cells or the viral etiology of cancer has been both studied and reviewed extensively. This text will help provide a general basis upon which a sound knowledge of oncology might be built.

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1. The nature of cancer

INTRODUCTION

The term cancer is really a generic name for a group of diseases that share a common type of disordered growth. It originates from the Latin word for crab, itself related to the Greek Καρκίνος (*karkinos*) meaning both crab and cancer, from which the term *carcinoma* is derived. Since the original Indo-European root *kar* meant hard, it is evident that the name is suggestive of a hard mass that spreads like the claws of a crab. Galen drew such an analogy nearly two thousand years ago, when he described cancer of the breast with its lateral prolongations of the tumor and the adjacent distended veins (1). Another term applied to cancer is *malignancy*, which refers to the lethal potential of this infiltrative disease and which distinguishes it from *benign tumors;* the latter lack the ability to spread by infiltration and metastasis and thus are not generally life-threatening. However, a benign tumor of the brain, for example, may be deadly, whereas a malignant skin tumor is often curable and thus presents little threat to life. The distinction, then, is certainly not an absolute one. Both these types of growth disorder give rise to tumors, a name that originally meant only a swelling and was thus applied also to inflammatory conditions.

Another term frequently used as a synonym for a cancer is *neoplasm*, although strictly, this only defines a condition as a new growth, that is, a tumor, without specifying whether it is benign or malignant. A number of other growth abnormalities distinguishable from both benign and malignant

tumors will be described in the next section. Our immediate purpose is to examine some general concepts and myths about cancer and to introduce some of the topics that will be covered later in this volume.

First we should examine the growth of cancer. There is a widespread conviction that cancer cells proliferate wildly at rates that are quite unlike those of normal tissues. Many, but not all tumors, do indeed exhibit very high growth rates, although it is doubtful if any can match the rate of cellular proliferation in normal bone marrow or intestinal mucosa. In such rapidly proliferating normal tissues, however, the whole process of cell division and replacement is regulated, so that no net accumulation of cells or disruption of tissue structure occurs. This state of dynamic equilibrium contrasts strongly with cancerous growth, in which cell division proceeds without any regard to the need for replacement, and occurs at the expense of normal tissue architecture, which invariably is disrupted in the process. Furthermore, to an extent that varies with the type of tumor, cells may be shed from the main mass and set up new foci of growth—*metastases*—at distant sites.

Another distinctive feature of cancer cells is that they may have lost properties that characterize the cells of their tissue of origin; that is, they are less differentiated. This loss of differentiation includes both morphological and biochemical markers, and may vary from minor deviations, which are barely detectable, to changes so major that the tissue of origin can no longer be identified with certainty. Conversely, cancer cells may acquire metabolic capabilities that are lacking in the parent tissue, such as the ability to elaborate what are known as ectopic hormones. This represents a derepression of gene loci, the activity of which is repressed in the parent cell line, that accompanies loss of differentiation. These distinctive features have been assembled into the concept of tumor progression formulated by Foulds (2). Early tumors are envisaged as being relatively responsive to such host control mechanisms as hormones. Later, as normal features are lost, the responsiveness also disappears, apparently irreversibly, and a stage of independent growth is reached when the tumor spreads freely. Most abnormal growth processes—hyperplasias, benign tumors, and metaplasias—never attain the stage of uncontrolled growth.

The reasons for the most singular characteristic of cancer, its ability to kill those who contract it, are complex. Obstruction of vital functions and disruption of needed organ structure, obvious results of tumor growth, may cause death in those with malignant, or for that matter benign tumors. These, however, are not the most frequent causes of death. Other factors

such as malnutrition, cachexia, increased susceptibility to infection, hemorrhage, endocrine disturbances, production of toxins, psychological problems, and the side effects of therapy contribute to the death of a patient.

Recent public pronouncements emphasizing the dangers from environmental carcinogens are based on an assumption that 80 percent or more of human cancer results from exposure to such agents, including dietary items, and is preventable. The claim is based on analysis of worldwide cancer incidence data, in which the lowest figures are taken as the norm (3,4). As we shall see in the next chapter, the death rate from cancer has increased throughout this century (see Figure 2-4). Although much of this increase may be explained by such factors as a fall in mortality from infectious diseases, an altered population with relatively more older people, and better reporting of mortality information, it is likely that there has been a significant increase in the true incidence of cancer. Thus, in the United States, as in other industrialized countries, cancer is now the second major cause of death. In less industrialized societies, lower death rates from malignant disease may reflect shorter life expectancies, the prevalence of infectious diseases, and inadequate data gathering, but it is likely that lower levels of toxic industrial wastes, and other differences affecting life-styles, also contribute. A related epidemiological finding is the wide variation in the incidence of individual types of cancer when different societies are compared. Such variations reflect underlying differences in the spectra of carcinogens to which the populations are exposed, genetic features, infections, diet, amount of stress in daily life, and other personal and cultural factors. Increasing emphasis is now being placed on the epidemiology and etiology of cancer with a view toward reducing the incidence of this disease.

Despite its prevalence, until recently cancer was surrounded by a quite extraordinary secrecy that was intended to protect the patient from knowledge of his or her poor prognosis and to prevent the personal tragedy from becoming public. This was done mainly from consideration for the patient and the family, but also because in the minds of many people a feeling of shame was associated with the disease. The very magnitude of the problem, however, and the slow, but steady progress achieved in treatment, have forced a reevaluation of this secrecy, which usually worked to the detriment of the patient by discouraging early treatment and causing needless anguish. These changed attitudes are typified by the way several prominent victims of cancer have deliberately publicized the nature and treatment of their disease. Such examples serve an educational purpose for

Table 1-1 Incidence of major solid tumors for the U.S. white population per 100,000, and 5-year survival rates for indicated decades.

		Incidence		*Five-year survival in percent*		
Site	*Sex*	1947	1969	1940–49	1950–59	1960–69
Bladder	M	16.3	19.7	41	55	59
	F	7.0	5.2	44	53	58
Breast	F	70.0	72.5	53	60	63
Colon	M	23.4	29.6	29	42	43
	F	25.2	25.0	35	46	46
Lung	M	28.7	67.0	3	7	8
	F	6.5	13.5	8	11	12
Ovary	F	14.7	13.3	25	29	33
Pancreas	M	8.8	10.7	1	1	1
	F	5.6	6.8	2	2	2
Prostate	M	36.4	44.7	37	47	54
Stomach	M	31.4	12.9	9	12	11
	F	17.3	5.8	9	13	14
Uterus	F	60.7	38.1	54	65	65

Data derived from E. Silverberg and A. I. Holleb: Major trends in cancer: 25 year survey. CA-A Cancer Journal for Clinicians 25:2 (1975).

those not aware of the capabilities of current therapy, although harm also may result when recourse to unproven remedies is publicized.

Although significant progress has been made recently toward curing some kinds of cancer, treatment of the more common solid tumors has not dramatically improved cure rates over the period 1940 to 1969 (Table 1-1). This has led many to frustration with orthodox medical therapy and recourse to unconventional treatments. Some of these, which stress dietary supplements, are not unreasonable in themselves, in view of the poor nutritional status of many cancer patients, but others rely on drugs or procedures with no evidence of value or efficacy. Unfortunately, a natural desire to explore any possible cure has all too frequently caused those suffering from cancer to become victims of fraud and deceit.

More research into both prevention and treatment is clearly needed if progress is to be made toward further marked reductions in deaths from cancer. Thus we must redefine goals and develop alternate approaches, since a criticism that has been leveled against current research endeavors is that too many funds have been spent on costly and relatively ineffective human application of therapy. An analogous situation would be one in which polio was still being treated with ever more elaborate and costly

supportive devices for maintaining paralyzed victims, while approaches aimed at controlling the virus responsible for the disease were ignored. As will become evident in this book, such an attitude to cancer research is no longer justified, if indeed it ever was, since most researchers are very alert to any new approach, if only to keep up in a very competitive field.

CLASSIFICATION OF TUMORS AND GROWTH DISORDERS

We have introduced a few of the more common terms that relate to growth abnormalities at the beginning of this chapter. Now it is appropriate to discuss these and other terms more comprehensively. As the reader will recall, the tissues derived from the *mesoderm* or middle germ layer in embryonic development are basically *connective and supportive tissues*, whereas *epithelial* organs and the *nervous system* arise from the *endoderm* and *ectoderm*. Tissues of mesodermal origin (*mesenchymal* tissues) account for up to 80 percent of the mass of an animal, including as they do such major structures as bones, tendons, muscles, cartilage, and fat. They also provide a structural basis for epithelial tissues. Apart from various epithelia, parenchymal organs, such as the liver, salivary glands, mammary glands and the nervous system, are primarily of epithelial origin. This distinction between tissue classes is carried over into all forms of abnormal growths. It is interesting that, although normal tissues are predominantly mesenchymal, abnormal growth phenomena, such as tumors, are far more commonly of epithelial origin, indicating that these tissues may have up to 50 times greater incidence of malignant transformation of their cells. This probably reflects the fact that it is the epithelia that are the primary areas of interaction with the environment and its carcinogenic influences.

Several growth disorders do not normally form tumors and thus may be distinguished from malignant and benign neoplasms. In *hyperplasia*, there is excessive proliferation of all the normal cellular elements, which retain an essentially normal appearance, with only a minimal degree of immaturity evident. In Figure 1-1, skin hyperplasia, such as would result from stimulation by a chemical or mechanical irritant, is illustrated schematically. New cell production exceeds cell destruction, with mitoses occurring in the higher layers as well as in the basal layers of the skin. Eventually, increased production of the horny layer, which is sloughed off, increases the rate of cell loss and brings the process back into the original equilibrium state, provided there is not a perpetuation of the stimulus. Psoriasis is in some respects a sustained hyperplasia, with an increased cell turnover