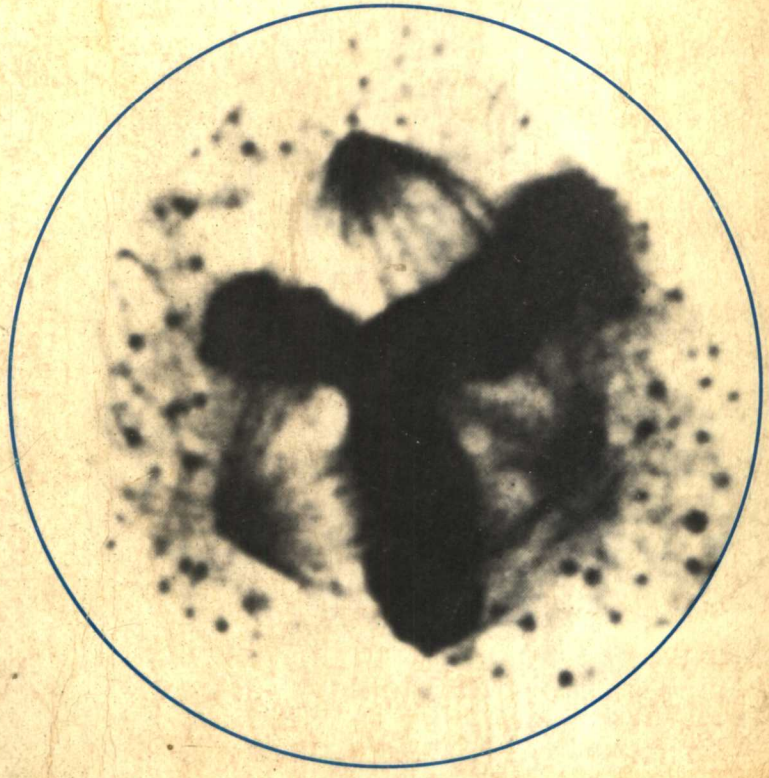
RAYMOND W. RUDDON

CANCER BIOLOGY



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Preface

This book is meant to provide a concise, yet comprehensive review of cancer biology from basic mechanisms of carcinogenesis to the etiology and pathophysiology of human cancer. The emphasis is on the molecular mechanisms involved in the malignant transformation of cells and in the pathological changes that occur in an experimental animal or a patient with cancer. Evidence for and against the various proposed causes of cancer is presented and discussed. The book is intended for graduate students in biological and medical sciences, medical students, advanced undergraduate students in biology, and nurses and physicians working in the field of oncology. It is anticipated that experts in various aspects of cancer research will also find it a useful text. I have referenced the papers that were keys to the early development of a research area, as well as those that made fundamental advances possible, so that the reader can see how an area developed and in what direction it is heading. Where available, references to clinical studies that relate to the biological events of malignant transformation observed in cultured cells or animals, or that suggest potential diagnostic or therapeutic applications of these events, have been included.

The seed for the motivation to write this book was probably planted one day during a conversation with a graduate student who was coming to work in my laboratory. I, of course, expected him to become a cancer biologist, quickly. Thus, he asked me if I could provide a textbook or a few articles that would give him an overview of cancer, what causes it, what the path-

ological changes are, what is known about the biochemistry of the cancer cell, etc. I began to list the subjects that I thought he should know something about, which included the pathological classification of neoplasms, cancer epidemiology, chemical carcinogenesis, viral carcinogenesis, tumor immunology, cellular differentiation, growth factors, cyclic nucleotides, phosphorylation mechanisms, DNA repair, and host-tumor interactions. In addition, I felt strongly that he should learn the salient features of the disease process at both the cellular and whole organism level. Other books, some of them quite good, have attempted to provide this sort of information. However, they are generally written by several authors who have different expertise and differing points of view. This has the advantage of providing the view of the expert in a given area, but the disadvantage of not linking one topic with another. It is hoped that an advantage of this book will be its integrated approach to the malignant alterations observed in individual cells and whole organisms, including man.

I am deeply indebted to the scientists who allowed me to utilize data from their own research to make various points in the text. I also wish to thank Drs. William Pratt, Richard Roblin, and Josh Fidler, who reviewed parts of the manuscript and made valuable suggestions, and Dr. Raymond Gilden, who provided information on the classification of RNA tumor viruses. I am greatly indebted to Sally Miller for preparation of the manuscript, and I thank Jo Ann Tichnell for her help in proofreading and indexing the text.

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1. Nature of malignant tumors

CHARACTERISTICS OF MALIGNANT TUMOR CELLS *IN VIVO*

Malignant neoplasms or cancers have several distinguishing features that enable the pathologist or experimental cancer biologist to characterize them as abnormal. The most common types of human neoplasms derive from epithelium, that is, the cells covering internal or external surfaces of the body. These cells have a supportive stroma of blood vessels and connective tissue. Malignant neoplasms may resemble normal tissues, at least in the early phases of their growth and development. Neoplastic cells can develop in any tissue of the body that contains cells capable of cell division. Though they may grow fast or slowly, their growth rate frequently exceeds that of the surrounding normal tissue. This is not an invariant property, however, since the rate of cell renewal in a number of normal tissues (e.g., gastrointestinal tract epithelium, bone marrow, and hair follicles) is as rapid as that of a rapidly growing tumor.

The term "neoplasm", meaning new growth, is often used interchangeably with the term "tumor" to signify a cancerous growth. It is important to keep in mind, however, that tumors are of two basic types: benign and malignant. The ability to distinguish between benign and malignant tumors is crucial in determining the appropriate treatment and prognosis of a patient who has a tumor. The features that differentiate a malignant tumor from a benign tumor are listed below.

1. Malignant tumors invade and destroy adjacent normal tissue; benign tumors grow by expansion, are usually encapsulated, and do not invade surrounding tissue. Benign tumors may, however, push aside normal tissue and may become life-threatening if they press on nerves or blood vessels or if they secrete biologically active substances, such as hormones that alter normal homeostatic mechanisms.

2. Malignant tumors metastasize via lymphatic channels or blood vessels to lymph nodes and other tissues in the body. Benign tumors remain localized and do not metastasize.

3. Malignant tumor cells tend to be "anaplastic" or less well differentiated than normal cells of the tissue in which they arise. Benign tumors usually resemble normal tissue more closely than malignant tumors do.

Some malignant neoplastic cells maintain a structural and functional resemblance to the normal tissue in which they arise. Later, as the malignant neoplasm progresses, invades surrounding tissues, and metastasizes, the malignant cells may bear less resemblance to the normal cell of origin. The development of a less well differentiated malignant cell in a populaton of differentiated normal cells is sometimes called "dedifferentiation." This term is probably a misnomer for the process, since it implies that a differentiated cell goes backwards in its developmental process after carcinogenic insult. It is more likely that the anaplastic malignant cell type arises from the progeny of a tissue "stem cell" (one that still has a capacity for renewal and is not yet fully differentiated), which has been blocked or diverted in its pathway to form a fully differentiated cell.

Examples of neoplasms that maintain a modicum of differentiation include islet cell tumors of the pancreas that still make insulin, colonic adenocarcinoma cells that form gland-like epithelial structures and secrete mucin, and breast carcinomas that make abortive attempts to form structures resembling mammary gland ducts. Hormone-producing tumors, however, do not respond to feedback controls regulating normal tissue gowth or to negative physiological feedback regulating hormonal secretion. For example, an islet cell tumor may continue to secrete insulin in the face of extreme hypoglycemia, and an ectopic ACTH-producing lung carcinoma may continue to produce ACTH even though circulating levels of adrenocortical steroids are sufficient to cause Cushing's syndrome (see Chapter 6). Many malignant neoplasms, particularly the more rapidly growing and invasive ones, only vaguely resemble their normal counterpart tissue structurally and functionally. They are thus said to be "undifferentiated."

4. Malignant tumors usually grow more rapidly than benign tumors. This is not invariably the case, but malignant tumors, once they reach a clinically detectable stage, generally show evidence of significant growth, with involvement of surrounding tissue, over weeks or months, whereas benign tumors often grow slowly over several years.

Malignant neoplasms continue to grow even in the face of starvation of the host; they press on and invade surrounding tissues, often interrupting vital functions; they metastasize to vital organs, for example, brain, spine, and bone marrow, compromising their functions; and they invade blood vessels, causing bleeding. The most common effects on the patient are cachexia (extreme body wasting), hemorrhage, and infection. About 50% of terminal cancer patients die from infection (see Chapter 7).

Differential diagnosis of cancer from a benign tumor or a nonneoplastic disease usually involves obtaining a tissue specimen by biopsy, surgical excision, or exfoliative cytology. The latter is an examination of cells obtained from swabbings, washings, or secretions of a tissue suspected to harbor cancer; the "Pap test" involves such an examination. The cytological criteria that enable the pathologist to confirm the diagnosis or at least to suspect that cancer is present (thus indicating the need for further diagnostic tests) are as follows:

1. The morphology of cancer cells is usually different and more variable than their counterpart normal cells from the same tissue. Cancer cells are more variable in size and shape (Figure 1-1).

2. The nucleus of cancer cells is often larger and the chromatin more apparent ("hyperchromatic") than in normal cells; the nuclear/cytoplasmic ratio is often higher; and the cancer cell nuclei contain prominent, large nuceoli (Figure 1-1).

3. The number of cells undergoing mitosis is usually greater in a population of cancer cells than in a normal tissue population. Twenty or more mitotic figures per 1000 cells would not be an uncommon finding in cancerous tissue, whereas under one per 1000 is usual for benign tumors or normal tissue.[1] This, of course, would be higher in normal tissues that have a high growth rate, such as bone marrow and crypt cells of the gastrointestinal mucosa.

4. Abnormal mitoses and "giant cells," with large, pleomorphic (variable size and shape) or multiple nuclei, are much more frequent in malignant tissue than in normal tissue (Figure 1-2).

5. An abnormal number or arrangement of chromosomes may occur in

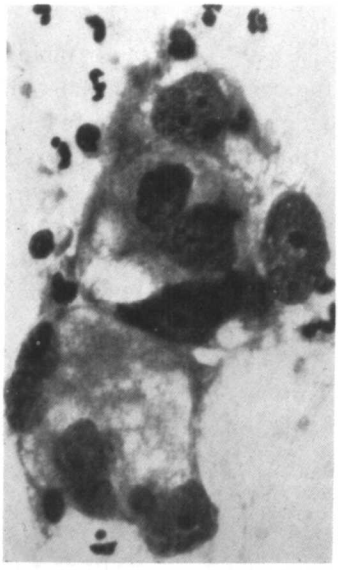

Figure 1-1 Malignant cells in vaginal secretion prepared by Papanicolaou technique. Note abnormal size and shape of cells, density of chromatin in nuclei, and prominent nucleoli. Numerous polymorphonuclear leukocytes are also present (X650). (From Warren.[1])

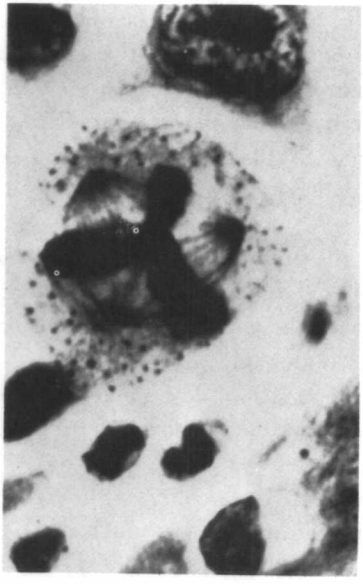

Figure 1-2 Abnormal tripolar mitosis occurring in malignant melanoma. (Phosphotungstic acid-hematoxylin stain; X2350). (From Warren.[1])

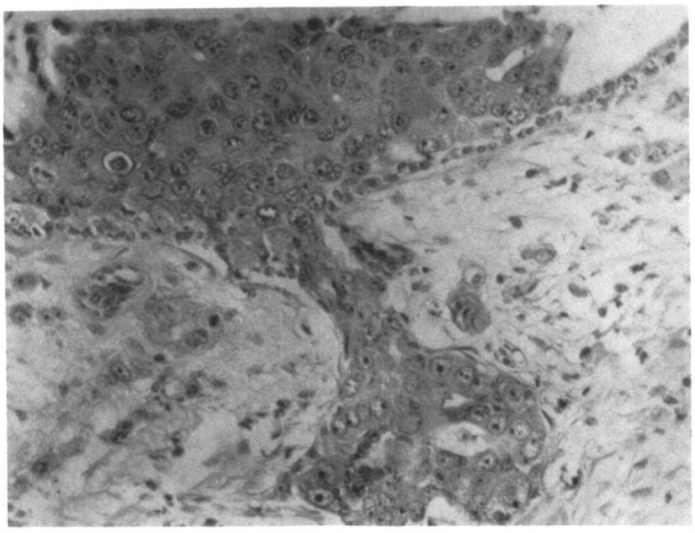

Figure 1-3 Mammary carcinoma invading surrounding breast tissue in a 32-year-old woman (X400). (From Warren.[1])

malignant cells. For example, the Philadelphia chromosome, the result of a translocation of a piece of chromosome 22 to chromosome 9, is present in a high percentage of patients with chronic myelocytic leukemia.

Certain of the above cytological "markers" of malignancy may also be present to some extent in tissues damaged by nonmalignant disease processes or by physical or chemical toxic agents, particularly if cell turnover is high and tissue repair rapid. To establish the diagnosis of malignancy, therefore, the clinical status of the patient must also be considered, including family history, age, symptoms that might relate to tissue invasion or metastasis, and results of other diagnostic tests. The clearest evidence, of course, would be a tissue specimen that shows invasion of surrounding normal tissue (Figure 1-3) or the presence of malignant cells in metastatic sites, e.g., lymph nodes draining the involved tissue.

CLASSIFICATION OF HUMAN TUMORS

Current, rapidly expanding medical technology has produced improvements in diagnostic testing, such as fiberoptic instruments for endoscopic examination, angiography, ultrasonography, and computerized axial tomography (CAT) scans. It is still true, however, that the only certain diag-

nosis of cancer is based on careful histological examination of tissues by a competent pathologist. What these recent advances have done, really, is to improve dramatically the oncologist's ability to obtain tissues for examination and to identify small, potentially cancerous lesions in previously inaccessible sites in the body.

The classification of human tumors is based upon the following:

1. Anatomical site of primary tumor and metastasis (e.g., lung, breast, colon)
2. Tissue type and histological classification
3. Histological grade of malignancy
4. Extent of tumor progression (size and degree of invasion and metastatic spread)

The correct classification of a neoplasm is crucial to determining the patient's prognosis, the type of therapy, and the intensity and duration of therapy.

Anatomical site

The site of the tumor dictates several things about the clinical course of the tumor including (i) the likelihood and route of metastatic spread, (ii) the effects of the tumor on body functions, and (iii) the type of treatment that can be employed. It is also important to determine whether the observed tumor mass is the primary site (i.e., tissue of origin) of the tumor or a metastasis. A primary epidermoid carcinoma of the lung, for example, would be treated differently and have a different prognosis than an embryonal carcinoma of the testis metastatic to the lung. It is not always easy to determine the primary site of a neoplasm, particularly if the tumor cells are undifferentiated. The first signs of a metastatic tumor may be a mass in the lung noted on X-ray or a spontaneous fracture of a vertebra that had been invaded by cancer cells. Since the lungs and bones are frequent sites of metastases for a variety of tumors, the origin of the primary tumor may not be readily evident. This is a very difficult clinical situation because to cure the patient or to produce long-term remission, the oncologist must be able to find and remove or destroy the primary tumor to prevent its continued growth and metastasis. If histological examination does not reveal the source of the primary tumor, or if other diagnostic techniques fail to

reveal other tumor masses, the clinician has to treat blindly and thus he might not choose the best mode of therapy.

Another consideration is the accessibility of a tumor. If a tumor is surgically inaccessible or too close to vital organs to allow complete resection, surgical removal is impossible. For example, a cancer of the common bile duct or head of the pancreas is often inoperable by the time it is diagnosed because these tumors invade and attach themselves to vital structures early, thus preventing curative resection. Similarly, if administered anticancer drugs cannot easily reach the tumor site, as is the case with tumors growing in the pleural cavity or in the brain, these agents might not be able to penetrate in sufficient quantities to kill the tumor cells.

The site of the primary tumor also frequently determines the mode of, and target organs for, metastatic spread. For example, carcinomas of the lung most frequently metastasize to regional lymph nodes, pleura, diaphragm, liver, bone, kidneys, adrenals, brain, thyroid, and spleen. Carcinomas of the colon metastasize most commonly to regional lymph nodes, liver, and by local extension, they ulcerate and obstruct the gastrointestinal tract. Breast carcinomas most frequently spread to axillary lymph nodes, the opposite breast via lymphatic channels, lungs, pleura, liver, bone, adrenals, brain, and spleen. Cancers metastasize via lymphatic channels or blood vessels. The most frequent site of distant metastasis of colon carcinomas, for example, is the liver. This occurs via the portal vein, which receives much of the venous return from the colon and flows to the liver.

Some tissues are more frequent sites of metastasis than others. Due to their abundant blood and lymphatic supply, as well as their function as "filters" in the circulatory system, the lungs and the liver are the most common sites of metastasis from tumors occurring in visceral organs. Metastasis is usually the single most important criterion determining the patient's prognosis. In breast carcinoma, for example, the five-year survival rate for patients with localized disease and no evidence of axillary lymph node involvement is about 85%; but when more than four axillary nodes are involved, the five-year survival is about 30%, on the average.[2]

The anatomical site of a tumor will also determine its effect on vital functions. A lymphoma growing in the mediastinum may press on major blood vessels to produce the superior vena caval syndrome, manifested by edema of the neck and face, distention of veins of the neck, chest, and upper extremities, headache, dizziness, and fainting spells. Even a small tumor growing in the brain can produce such dramatic central nervous system

effects as localized weakness, sensory loss, aphasia, or epileptic-like seizures. A lung tumor growing close to a major bronchus will produce airway obstruction earlier than one growing in the periphery of the lung. A colon carcinoma may invade surrounding muscle layers of the colon and constrict the lumen, causing intestinal obstruction. One of the frequent symptoms of prostatic cancer is inability to urinate normally.

Tissue type and histological classification

The classification of human tumors by tissue type is given in Table 1-1. Although the terminology applied to neoplasms can be confusing for a number of reasons, certain generalizations can be made. The suffix *oma*, applied by itself to a tissue type, usually indicates a benign tumor. Some malignant neoplasms, however, may be designated by the *oma* suffix alone; these include lymphoma, melanoma, and thymoma. In this case, the term is frequently preceded by the word malignant, e.g., malignant lymphoma, malignant melanoma, etc. Rarely, the *oma* suffix may be used to describe a non-neoplastic condition such as granuloma, which is often not a true tumor, but a mass of granulation tissue resulting from chronic inflammation or abscess. Malignant tumors are indicated by the terms carcinoma (epithelial in origin) or sarcoma (mesenchymal in origin) preceded by the histological type and followed by the tissue of origin. Examples of these include adenocarcinoma of the breast, squamous cell carcinoma of the lung, basal cell carcinoma of skin, and leiomyosarcoma of the uterus. Most human malignancies arise from epithelial tissue. Those arising from nonglandular epithelium are usually squamous cell types, whereas those emanating from glandular epithelium are termed adenocarcinomas. When a malignant tumor no longer resembles the tissue of origin it may be called *anaplastic* or *undifferentiated*. If a tumor is metastatic from another tissue, it is designated, for example, an adenocarcinoma of the colon metastatic to liver. Some tumors arise from pluripotential primitive cell types and may contain several tissue elements. These include mixed mesenchymal tumors of the uterus, which contain carcinomatous and sarcomatous elements, and teratocarcinomas of the ovary, which may contain bone, cartilage, muscle, and glandular epithelium.

The histological classification of neoplasms determines the growth patterns, propensity to metastasize, type of treatment, and, thus, the prognosis. Several examples will serve to illustrate this.

Lung carcinomas fall into three general categories: (i) epidermoid or

Table 1-1 Classification of human tumors by tissue type.

Tissue of origin	*Benign*	*Malignant*
1. Epithelium		
Surface epithelium (nonglandular)	Papilloma	Carcinoma (squamous cell, epidermoid, transitional cell)
Glandular epithelium	Adenoma	Adenocarcinoma
Basal layer of epidermis	—	Basal cell carcinoma
Trophoblasts of placental villi	Hydatidiform mole	Choriocarcinoma
2. Connective tissue		
Fibrous tissue	Fibroma	Fibrosarcoma
Cartilage	Chondroma	Chondrosarcoma
Bone	Osteoma	Osteosarcoma
Smooth muscle	Leiomyoma	Leiomyosarcoma
Striated muscle	Rhabdomyoma	Rhabdomyosarcoma
Fat	Lipoma	Liposarcoma
3. Endothelial tissue and its derivatives		
Blood vessels	Hemangioma	Hemangiosarcoma
Lymph vessels	Lymphangioma	Lymphangiosarcoma
Bone marrow		
Granulocytes	—	Myelocytic leukemia
Erythrocytes	Polycythemia vera	Erythrocytic leukemia
Lymphocytes	Infectious mononucleosis	Lymphocytic leukemia
Plasma cells	—	Multiple myeloma
Monocytes	—	Monocytic leukemia
Endothelial lining	—	Ewing's sarcoma
Lymphoid tissue		Hodgkin's disease
		Non-Hodgkin's malignant lymphomas
		Lymphocytic type
		Histiocytic type
		Undifferentiated, pleiomorphic type
		Undifferentiated, Burkitt type
Thymus	—	Thymoma
4. Neural tissue and its derivatives		
Glial tissue	"Benign" gliomas (some ependymomas and oligodendrogliomas are considered nonmalignant)	Glioblastoma multiforme, medulloblastoma, astrocytoma, ependymoma, oligodendroglioma