

Cancer Cells



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ILLUSTRATED



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DEDICATED TO MY WIFE
ALICE SMITH COWDRY
*who advised me to enter
Cancer Research*

PREFACE

CANCER is a fascinating problem both from the biological and medical points of view. It focusses attention on cells both normal and malignant, for neither can be appreciated without knowledge of the other. Perhaps no other problem, except that of ageing, engages the attention of specialists in more fields of investigation.

Botanists are interested because certain long recognized, sharply localized overgrowths of plant tissue resemble benign and even malignant tumors. Bacteriologists see in the sudden change of a relatively harmless bacterium into a devastatingly virulent one a modification not without similarity to the malignant transformation by which previously normal cells become cancerous. Protozoologists engaged in a study of the change of normal paramecia into "killer paramecia" also have in mind the problem of carcinogenesis. Embryologists, dedicated to the investigation of normal growth, not infrequently find themselves trying to compare this with the malignant almost unrestrained growth of cancers. Geneticists, in their experimental researches on inheritance in many forms of life, have much to contribute to the elucidation of hereditary factors in cancer production. Some virologists point to cancers in amphibia, birds and mammals, some of which are unquestionably caused by viruses, and tenaciously advance the idea that all human cancers are likewise of virus etiology. They say "in animals why not also in man"? Pathologists and tissue culture experts are directly involved in the cancer problem. Biochemists, cytochemists and biophysicists have much to contribute. Physicians, surgeons and radiologists cure many early cancers; but, confronted by so many hopeless victims of this disease, they are alert to any new knowledge of the specific vulnerability of cancer cells which can supply clues to more effective diagnosis and treatment.

These cancer specialists and many others view the terrible antisocial behavior of cancer cells in terms of their own experience, as susceptible to investigation by the techniques they are accustomed to use. No single individual will ever be able to present adequately what is known about cancer cells. His background and training are sure to be deficient in respects too numerous to mention. Consequently, this attempt to bring together knowledge of cancer cells obtained by a wide range of specialists is offered with an apology for its shortcomings.

Deciding what to include and what to leave out is a constant problem

while one is writing and planning such a presentation. To consider cancer cells by themselves would obviously be shortsighted and worthless. They are what they are in consequence of their heredity and the highly diversified tissue fluid environments in which they live. These environments are subject to sudden and temporary as well as to slow and enduring chemical and physical alterations brought about by agents acting on the body from without as well as by many others of internal origin. There are billions of cellular vital units normally active living in a bewildering array of adjustments and maladjustments to their surroundings.

The available information on cancer cells increases much more rapidly than it can be even partially digested. Unless one immediately records what is thought to be really significant, it is displaced by the onrush of further data and forgotten. Writing this book is an instructive lesson of the need for bringing each line of evidence to some sort of conclusion before passing on to another aspect of cancer cells no matter how attractive. Winged fancy must not be permitted to roam unleashed.

In most cases no attempt is made to assess priorities. Many advances have been brought about by the insight and labor of long lines of devoted investigators. To select one and leave out the others, unless all the circumstances have been weighed with meticulous care might be unfair. My policy generally is to refer to the most recent reports trusting the authors to list their own previous papers on the subject as well as those by others. The purpose is to introduce the reader to the more important facts about cancer cells, to raise questions considered important, and, wherever possible, to supply clues as to how he can further explore the issues for himself. Since his time is valuable, the literature references are complete. Given the date, the title in the original language and the size of the paper (first and last page numbers) it is up to him to decide whether he wants to locate and consult a book or journal not present in his local institutional library. The authors are listed alphabetically in a single bibliography, for it is confusing, and results in many duplications, to supply references at the end of each chapter. Because proceedings of cancer societies, tumor registries, vital statistics, reports of the World Health Organization and other valuable references are not always printed under the heading of the individual writers, these are brought together in an appendix before the authors' bibliography.

The order of presentation of what is known and suspected about cancer cells should be logical and constructive, each chapter constituting more or less of a unit, carrying the account a step farther and supplying a basis for what comes next. This is easier said than done.

No chapter can be a self-contained unit, for knowledge of cancer cannot be compartmentalized. One can only consider certain aspects of cancer cells primarily in separate chapters and bring in supplementary information in others. The order of presentation was changed again and again as the writing progressed in efforts to gain some measure of continuity.

Finally it was decided to begin with an explanation of the distinction between malignant and benign tumors—Chapter 1.

To mention some of the properties of malignant cells—Chapters 2 to 5.

To give examples of the distribution of malignant potentialities in normal cells, of the agents that are capable of bringing about malignant transformations and the theories concerning their actions—Chapters 6 to 10.

To discuss the susceptibility of normal cells to these carcinogens—Chapters 11 to 13.

To consider the latent period and factors that modify the production of cancers—Chapters 14 to 16.

To outline briefly data on diagnosis, prevention and treatment of cancer—Chapters 17 to 18.

To give a few reasons for optimism and to discuss some achievements and handicaps in cancer research—Chapters 19 to 20.

In many chapters I am open to criticism for straying from an account strictly limited to cancer cells. In this, I have followed my interests which include conditions of all sorts directly or indirectly influencing origin and fate of cancer cells. This book is moreover uneven chiefly because my training is uneven and especially inadequate in clinical medicine, physics and chemistry. Fortunately, my associate, Dr. Eugene Roberts, has helped me in writing the chapter on the chemical properties of cancer cells. But everyone will admit that no single individual can take the place of all of the specialists now investigating cancer. The following account is merely what one person interested primarily in cells and their activities has to say about cancer cells today.

Sometimes I have given without using quotation marks opinions and views which I have myself expressed in my previous publications. I have particularly in mind my "Textbook of Histology" (Lea & Febiger), my "Problems of Ageing" (Williams & Wilkins), my Presidential address to the American Association for Cancer Research (Cancer Research, Inc.) and my reports as United States Representative to the International Cancer Research Commission (*Acta Unionis Internationalis Contra Cancrum*). I am indebted to these publishers for the use of this material. I am thankful to my present publishers, W. B. Saunders Company, for the patience with which they have waited during the long years consumed in writing this book and the excellency of its format and printing.

I am also grateful to Mrs. Maude Hennessey for carefully checking literature references and for expert and cheerful assistance throughout to my secretary, Mrs. Tess Bresnahan.

E. V. COWDRY

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CHAPTER 1

CANCERS DEFINED

TO SAY THAT all cancers are death-dealing tumors is not sufficient. We may never know exactly what they are; but, as more knowledge about them accumulates, the day approaches when we shall be able to cure even advanced cancers. In the meantime we should be careful in the choice of terms so that our meaning will be clear. For an eloquent account of the difficulty of defining the term *cancer* see Willis (1952).

MALIGNANT NEOPLASMS

If you ask a number of cancer specialists to give a clear-cut definition of cancer they start out glibly and soon become involved. The usual definition is: *Cancer is a malignant neoplasm*. Let us examine the words: *Cancer*, *malignant* and *neoplasm*.

Cancer is a Latin word meaning a crab. The extensions into the surrounding skin from a primary cancer were thought to bear some resemblance to the legs extending out from the body of a crab, an animal which had the distinction of being one of the signs of the Zodiac. The Greek word for crab, *karkinos*, and the Sanscrit word, *karkara*, are related.

Malignant is an adjective having many meanings. Used in connection with neoplasm it implies resistance to treatment, a strong tendency to grow worse and fatal termination. Hypertension is also malignant when it exhibits these three features. But obviously in malignant neoplasms and in cases of malignant hypertension these features result from different underlying causes.

Neoplasm (G. *neos*, new + *plasma*, a thing formed) signifies a new growth. Cancer is truly a new growth insofar that the cells having become cancerous grow in a new and different way from their nonmalignant ancestors. The term neoplasm is more explicit than the word tumor, for the latter can be any swelling. Some neoplasms are malignant while others are benign. Leukemia is a malignant neoplasm of white blood cells. The cells grow in a new and unrestrained way and do not mature properly. There is usually a distinct accompanying enlargement, or swelling, of lymph nodes.

If then, we accept the definition of cancer as a malignant neoplasm, does it follow that all malignant tumors are cancers? Not necessarily. The term "cancer" can be used either in the broad sense to include all malignant neoplasms or equally correctly to include only malignant neoplasms of epithelial cells. It will be recalled that all epithelial cells are derivations of ectoderm

or endoderm and are by nature surface cells limiting either external surfaces of the body or surfaces folded into or extending into the substance of the body, connections with the external surface often being lost in the course of development as in the case of nerve cells. When one wishes to imply cancer in this narrow sense, it is advisable to designate the neoplasm as a carcinoma which is by definition an epithelial cancer.

Other malignant neoplasms included with carcinomas under the general heading of cancer are derived from cells of the middle germ layer, or mesoderm. The cells of origin are characteristically not surface, but "between cells" despite the fact that in the area between ectoderm and endoderm fluid can accumulate and be limited by flattened cells constituting a surface. The mesothelial cells of the serous cavities are of this category and entirely distinct from the epithelial cells lining cavities communicating with the external environment. The "between cells" of bone, and of the connecting tissue making up most of the flesh of the body, can give rise to malignant tumors commonly known as sarcomas (*G. sarx*, flesh, and *oma*, a swelling).

But it is not only from either ectoderm or mesoderm that malignant tumors arise. The so-called *mixed tumors* are derived from cells of more than one germ layer or more than one derivation of a single germ layer.

Still other malignant neoplasms, likewise often referred to as cancers, are the teratomas which include multiplying cells from all germ layers, ectoderm, mesoderm and endoderm, though not all of them may be behaving in a malignant fashion. The term is derived from the *G. teras*, a monster and *oma*, a swelling, because like an abnormal, misshapened fetus, it is a swelling consisting of cells of all three embryonic types. Though most teratomas arise in the male or female gonads they may occasionally develop in other sites.

NOMENCLATURE

It is convenient to use the term *cancer* in a general way as meaning any one of many malignant neoplasms. The Committee on Nomenclature of the International Cancer Research Commission under the Presidency of Dr. V. R. Khanolkar (Indian Cancer Research Centre, Parel, Bombay) is working out a series of terms which we hope will be acceptable to all nations.

The most valuable records of cancer deaths in the United States are contained in "Vital Statistics of the U. S." which are published each year in Washington, D. C. The terms now employed in these are recommended. They are thus included in Volume I of a "Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death" prepared by the World Health Organization and published in Geneva (1948). Owing to the vast amount of work required, "Vital Statistics of the U. S." becomes available only about two years after the year subjected to statistical analysis. Thus the report for 1949 appeared in the fall of 1951. In it deaths from cancer were listed under the heading of "malignant neoplasms, including neoplasms of lymphatic and hematopoietic tissues" and amounted to 206,325. These are classified under many headings. A convenient source of cancer