FUNDAMENTALS OF ONCOLOGY

Third Edition
Revised and Expanded

Henry C. Pitot

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Preface to the Third Edition

Since the manuscript for the second edition of this text was completed, information regarding the science of oncology, in the human and the experimental animal as well as in the plant kingdom, has expanded in an astounding manner. The prediction of an earlier reviewer that this text would require constant updating has proven true many times over. Furthermore, for the sake of our students—the prime motivation for writing this text—a reasonably succinct survey of the field of experimental oncology and its applications to humans continues to be of primary importance in our basic instructional program.

In this revision of the text, a number of new chapters have been added. A new Chapter 5, concerned with hereditary factors in the causation of cancer, has been included. The discussion of human cancer has been divided into two chapters: Chapter 9 is concerned with the direct known causes and Chapter 10 with the scientific and societal considerations of human cancer. Finally, the chapter on the biochemistry of neoplasia (Chapter 10 in the second edition) has also been divided into two chapters, one dealing with the biochemistry of the neoplastic transformation in vivo (Chapter 12), the other with the biochemistry and molecular biology of the neoplastic transformation in vitro (Chapter 13).

At the suggestion of one of the reviewers of the second edition, we have cited the references in the text for the convenience of the reader. This has the disadvantage of a somewhat more formal presentation, but we hope that it will be useful to the student who wishes to study the field of experimental oncology in greater depth. This fundamental text is not exhaustive in its treatment of the literature but presents representative examples of each of the topics and areas covered. My apologies to any colleagues whose work was not specifically

cited. If anyone feels strongly that additional references are needed, please communicate your suggestions to the author.

Again I would like to express my sincere appreciation to my colleagues at the McArdle Laboratory who read and made critical comments on the manuscript, especially Doctors Norman Drinkwater, Janet Mertz, James and Elizabeth Miller, Gerald C. Mueller, Van R. Potter, Rex Risser, Jeffrey Ross, Bill Sugden, and Howard M. Temin, and to Dr. Paul Carbone of the Wisconsin Clinical Cancer Center. In particular I would like to express my thanks to Dr. Ilse Riegel and Bette Sheehan for their invaluable help in editing and correcting the manuscript throughout all of its stages, and my appreciation to Mary Jo Markham and Karen Denk for their patient and expert transcribing and typing. Finally, my thanks are extended to Carol Dizack for her expert artistry in drawing the figures added to this edition of the text and to Terrill P. Stewart for his photographic skills.

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Preface to the Second Edition

In the few short years since the publication of the first edition of this text, a number of significant facts have been uncovered in the science of oncology. Many of these findings have been incorporated into the teaching of our basic course in experimental oncology through additional notes and lectures, and the revision of this text became a clear necessity.

In this revision we have maintained the same format as in the first edition but have altered the contents of most of the chapters, adding both figures and tables. In addition, the pathogenesis of cancer and the natural history of cancer in vivo have been divided into Chapters 6 and 8 respectively. Finally, Chapter 13 has been added to present some aspects of the basis for cancer chemotherapy. Although this chapter is not an attempt to discuss the various treatment modalities used in cancer therapy, the subject matter does introduce the student to the experimental basis for chemotherapy and also briefly discusses the methodology and rationale for the chemical therapies used today.

We have continued to utilize illustrative slides to supplement the lectures and text. Lectures by several of my clinical colleagues on the diagnosis, therapy, and psychosocial aspects of cancer continue to be significant components of our course.

Again I would like to express my sincere appreciation to a number of my colleagues at the McArdle Laboratory, especially Doctors Roswell Boutwell, James and Elizabeth Miller, Van R. Potter, Rex Risser, Bill Sugden, and Howard Temin, as well as others who have read and made critical comments on the manuscript. In particular, I would like to express my thanks to Dr. Ilse Riegel and Ms. Bette Sheehan for their invaluable help in collating, editing, and correcting the manuscript throughout all of its stages, and my appreciation to Ms. Karen

Preface to the First Edition

The sensationalism and publicity directed toward the investigation, diagnosis, and treatment of cancer as a disease in the human being have reached a dramatic level in the United States. In part this is a result of the decision by the political administration of Richard M. Nixon to make the conquest of cancer a major goal of his office. Although it is not my desire nor is this the place to consider the ramifications of this decision and the subsequent difficulties that have arisen in its implementation, it is clear that cancer research received a "shot in the arm" of international proportions by political decisions at the beginning of this decade. The U.S. public, who have supported the National Cancer Plan through their taxes, have been repeatedly apprised of its existence and progress since its inception in 1970. Much has been written on the subject of cancer in the scientific literature as a direct result of the financial impetus given to research in oncology over the past decade. A variety of books and monographs on the general subject of cancer in humans and animals for both the scientist and the layman have appeared during this same period.

This text is not meant to be a popular account of the cancer problem. More than two decades ago, the Department of Oncology, which comprises the McArdle Laboratory for Cancer Research of the University of Wisconsin at Madison, initiated a graduate course in oncology. This course consisted of a series of lectures covering a variety of aspects of experimental oncology including chemical and biological carcinogenesis, host-tumor relationships, the natural history of cancer, and the biochemistry of cancer. In addition, within a few years of its inception, several lectures were given on the diagnosis and therapy of cancer in the human patient. The course was and always has been oriented primarily toward the graduate student in oncology rather than speci-

fically for the medical student or postgraduate physician. In part as a result of the increased interest in cancer research by both graduate and undergraduate students and as part of the mechanism of self-evaluation of teaching programs, several years ago the McArdle Laboratory expanded its original course into three separate courses in experimental oncology. The first course in this series is open to all students and fellows at the University of Wisconsin, and the notes given to the students comprise the basis for this short text on the fundamentals of oncology.

During the course period, these notes are supplemented by several sessions in which slides are shown depicting a variety of examples both from human and animal neoplasms to illustrate many of the specific points presented in the text. A list of these slides can be made available to anyone interested, on written request to the author. In addition, at the end of the course several lectures are given to the students on the diagnosis and therapy of human cancer as well as on the psychosocial aspects and bioethics of human oncology.

It is the hope of those of us in the McArdle Laboratory involved in the teaching of this course that we can instill in our students the basic concepts of the science of this disease and thereby interest them in learning more about the mechanisms of neoplastic disease and the use of such knowledge toward the ultimate control of cancer in the human patient.

In particular, I would like to express my appreciation to my colleagues in the McArdle Laboratory, especially Drs. James and Elizabeth Miller, Van R. Potter, Ilse L. Riegel, Bill Sugden, Howard M. Temin, and others who have read and made critical comments on this manuscript at its earlier stages. My thanks also go to the several outside reviewers of the manuscript whose suggestions resulted in an increased number of illustrations and the addition of the epilogue, and to Mr. John L. Shane, whose artistic skill produced the drawings of the figures.

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Denk for her patient and expert typing. Finally, my thanks are again extended to Mr. John L. Shane for his continued artistic aid in drawing the new figures for this text.

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Cancer: Yesterday and Today

At various periods throughout history, certain diseases have been greatly feared by humans. In biblical times the disease most feared and abhorred by the general population was leprosy. During the Middle Ages and the Renaissance in Europe, the dreaded disease was bubonic plague—the "black death." During the nineteenth century the major killer associated with the most human suffering was the "white death" or tuberculosis. In the twentieth century, especially as a result of the advances in microbiology and pharmacology, infectious diseases do not play the major role in "developed cultures" that they did in the past. Today the disease that strikes fear in the hearts of most laypersons is cancer. One of the more succinct descriptions emphasizing the impact of the fear of the disease was written in 1936 by Glenn Frank, then President of the University of Wisconsin, at a symposium on cancer at the University of Wisconsin School of Medicine.

> But not all these tragic consequences together are the worst evil wrought by cancer. For *everybody* that is *killed* by the *fact* of cancer, multiplied thousands of *minds* are *unnerved* by the *fear* of cancer. What cancer, as an unsolved mystery, does to the morale of millions who may never know its ravages is incalculable. This is an incidence of cancer that cannot be reached by the physician's medicaments, the surgeon's knife, or any organized advice against panic. Nothing but the actual conquest of cancer itself will remove this sword that today hangs over every head.*

*Quoted from the welcome by President Glenn Frank to participants in "A Symposium on Cancer," University of Wisconsin School of Medicine, Madison, Wisconsin, September 7–9, 1936. University of Wisconsin Press, Madison, 1938.

Although the United States was not the first country to make the conquest of cancer a national effort, the government's financial backing of cancer research during the 1970s provided the greatest single impetus in the history of this country to the scientific search for knowledge and understanding of the control and elimination of cancer. In 1970, a special panel of consultants called together by the U.S. Senate submitted a report entitled "A National Program for the Conquest of Cancer" (1971); at the time it was perhaps the best summary of the status of cancer as a disease and of cancer research in this country. This report showed that cancer is the primary health concern of the people of the United States. In several polls, approximately two-thirds of those questioned admitted fearing cancer more than any other disease. Of 200 million Americans living in 1970, 50 million were destined to develop cancer, and approximately 34 million would die of the disease. According to the American Cancer Society, about 66 million Americans living in 1983 will eventually develop cancer. About one-half of all deaths due to cancer occur prior to the age of 65, and cancer causes more deaths among children under the age of 15 than any other disease. More than 16% of all deaths in this country are caused by cancer; it is second only to cardiovascular disease as the greatest killer of our population.

The committee of consultants pointed out that in 1969 the budget of this country, calculated on a per capita basis, provided $410 for national defense; $125 for the war in Vietnam; $19 for the space program; $19 for foreign aid; but only 89 cents for cancer research. During the same year, deaths from cancer were eight times the number of lives lost in the 6 years of the Vietnam War up to that time, five and one-half times the number of people killed in automobile accidents in that year, and greater than the number of servicemen killed in battle in all 4 years of World War II. Hodgson and Rice (1982) have indicated that the present yearly loss to this nation's economy because of cancer deaths is nearly $25 billion, with the cost of medical care of cancer patients in this country approaching $10 billion per year.

The 1970 report also indicated an increase in the incidence of cancer, partly because the population of older age groups is increasing. Clearly, cancer strikes more frequently in the older age groups. However, the major factor in the increased incidence is the sharp rise in lung cancer, attributable almost entirely to the "self-pollution" of cigarette smoking. The panel estimated that if Americans stopped smoking cigarettes, more than 15% of all cancer deaths in this country would be eliminated within several decades. The American Cancer Society estimated that there would be 126,000 deaths from lung cancer in 1985 in the United States.

Although we do not understand the basic nature of the neoplastic transformation, we know a great deal more about the disease today than we did 50 years ago. In 1930, the medical cure rate for those afflicted with cancer was about one in five. Today, approximately one in three is cured, and the panel esti-

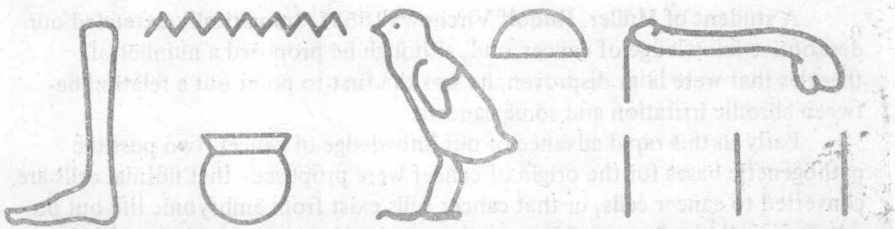
mated that this could be improved to almost one in two simply by better application of the knowledge that exists today. In fact, in 1982, the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program presented data to indicate that nearly 50% of white patients with cancer, excluding nonmelanoma skin cancer and carcinoma in situ (see Chapter 9), will survive to die of other diseases. Certain specific types of tumors that were 100% fatal prior to 1960 can now be cured in as many as 70% of the cases.

CANCER: YESTERDAY

In all likelihood, all multicellular organisms are afflicted, or have the potential to be afflicted, by the disease we call cancer. Paleopathologists have demonstrated that neoplastic lesions occurred in dinosaur bones long before the advent of *Homo sapiens* (Bett, 1957). In view of the numerous reports of both spontaneous and induced neoplasms in both plants and animals, vertebrates as well as invertebrates, it is quite probable that cancer has been with us for much of the evolutionary period of life on earth. Ancient Egyptians knew of the existence of cancer in humans, and in one papyrus a glyph clearly refers to a clinical tumor (Figure 1.1). In addition, autopsies of mummies have shown the existence of bone tumors and the probability of other neoplastic processes.

By the era of Hippocrates in the fourth century B.C., many types of neoplasms were clinically recognized and described, such as cancer of the stomach or uterus. Hippocrates coined the term *carcinoma,* which referred to tumors that spread and destroyed the patient. This was in contrast to the group he termed *carcinos,* which included benign tumors, hemorrhoids, and other chronic ulcerations. He proposed that cancer was a disease of an excess of black bile, which was manufactured by both the spleen and stomach but not the liver. This concept of the causation of cancer remained the predominant theory for almost

Figure 1.1 The symbol for "tumor" referring to the surgical treatment of cancer in the hieroglyphics of the Edwin Smith papyrus, dated to earlier than 1600 B.C. The reader is referred to Breasted's translation (1930) of the document for further information.



2000 years. Hippocrates also applied one of his cardinal rules, *primum non nocere* (first do no harm), to the treatment of cancer. Hippocrates as well as other physicians during the next two millennia tended not to treat ulcerated or deep-seated cancers.

Almost 600 years later, Galen distinguished "tumors according to nature," such as enlargement of the breast with normal female maturation; "tumors exceeding nature," which included the bony proliferation occurring during the reuniting of a fracture; and "tumors contrary to nature," which today we may define as neoplastic growths. This distinction, proposed some 1800 years ago, is still reasonably correct. Galen also suggested the similarity in gross outline between a crab and the disease we know today as cancer.

The concepts of Hippocrates and Galen dominated medical practice during the Middle Ages. With the advent of the Renaissance and during the seventeenth and eighteenth centuries, the "black bile" theory of causation of cancer was disputed by a number of physicians (including Ramazzini), and the surgery of neoplasms became somewhat more extensive. Several treatises on mastectomies for breast cancer, including dissection of regional lymph nodes, were written. Ramazzini attributed the high occurrence of breast cancer among nuns to the celibate life of these women. This was the first example of occupation-associated cancer, an observation that has withstood the test of time. In addition, in 1761, John Hill of London suggested that tobacco in the form of snuff was a cause of nasal polyps.

It was not until the nineteenth century, however, that physicians and scientists began to study cancer systematically and intensively. The anatomist Bichat extended the principles of Galen, which had reigned supreme for more than 1600 years. Bichat (1821) described the anatomy of many neoplasms in the human and suggested that cancer was an "accidental formation" of tissue built up in the same manner as any other portion of the organism. Seventeen years later, Johannes Müller (1838) extended the findings of Bichat by utilizing the microscope. Although the cellular theory was just being formulated during this period, Müller independently demonstrated that cancer tissue was made up of cells. At the time little was known about cell division, and Pasteur and others had not yet demonstrated the doctrine *omnis cellula e cellula*, that is, every cell from a cell.

A student of Müller, Rudolf Virchow (1863), dramatically extended our descriptive knowledge of cancer, and, although he proposed a number of theories that were later disproven, he was the first to point out a relation between chronic irritation and some cancers.

Early in this rapid advance of our knowledge of cancer, two possible pathogenetic bases for the origin of cancer were proposed—that normal cells are converted to cancer cells, or that cancer cells exist from embryonic life but do not express themselves until later in the organism's existence. Müller (1838)

supported the latter concept, as did Julius Cohnheim, who in 1877 advanced the "embryonal rest theory" of cancer. On the other hand, many pathologists such as Laënnec argued that a number of cancers resemble the normal tissues of the body and that "there are as many varieties of these as there are kinds of normal tissues." Laënnec did, however, recognize that a number of tumors bore no direct resemblance to any normal tissue found in the adult organism. Laënnec's studies supported the cellular theory (see above) and actually added to it the words *ejusdem naturae* which, combined with the original statement, may be translated as "every cell arises from a cell *of the same kind*" (cf. Shimkin, 1977).

In 1829, Recamier published *Recherches du Cancer*, in which he specifically introduced the term *metastases* and described clearly how cancer spreads by this method. Another major advance during this period was the demonstration by Waldeyer (1872) that metastases were the result of cell emboli. In addition, he was able to show that cells from primary cancer infiltrated blood and lymphatic vessels.

After major advances had been made in the knowledge of the biology of human neoplasia, experimental oncology emerged as a separate area of study. Experimental tumor transplantation was initiated shortly after the middle of the nineteenth century, and by 1900 some animal neoplasms had been carried through many generations of grafts with few alterations in the microscopic appearance of the neoplasms.

Students interested in a more detailed and readable discussion of some aspects of the history of the science of oncology are referred to Shimkin's *Contrary to Nature* (1977), which shows by extensive illustration and relatively complete documentation the development of oncology from ancient Egyptian times to many of the major discoveries of the last decade.

During the nineteenth century, many hypotheses of the origin and development of cancer were presented. In general, these hypotheses may be categorized as follows:

1. The irritation hypothesis
2. The embryonal hypothesis
3. The parasitic hypothesis

The first hypothesis encompassed what little was known at the time of the effects of chemical agents, mostly crude, and of radiation in the genesis of cancer. The relation of some ulcerations, both internal and external, to cancer appeared to support and strengthen this hypothesis. Scar cancers and those occurring after both acute and chronic injury were also cited in support of the irritation hypothesis.

Perhaps the most common example of cancer in support of the embryonal hypothesis is the nevus, or common mole of the skin. In most instances nevi are present from birth, and a very small percentage of such structures become

cancerous. Many neoplasms of embryonic tissue appearance, such as the teratoma occurring in the adult, also support this hypothesis.

Prior to the nineteenth century, Hippocrates' "black bile" theory of cancer causation served to inhibit any concepts of an infectious etiology of cancer. However, in view of the rapid advances made in our understanding of infectious disease during the last century by Pasteur and numerous others, physicians and scientists searched for an infectious origin of cancer during the last 100 years. Several reports appeared at the end of the nineteenth century, including that of Doven, who described a bacterium, *Micrococcus neoformans*, which he isolated from several neoplasms and believed to be the cause of all types of cancer (cf. Bett, 1957; Oberling, 1952). As it turned out, this organism was merely a common staphylococcus. It was not until the twentieth century that the "infectious" hypothesis became scientifically sound. Even with the dawn of this century, more than 50 years were to pass before proper scientific recognition was given to the parasitic hypothesis.

CANCER: TODAY

Cancer rose from the eighth most common cause of death in the United States in 1900 to the second most common cause by 1972, second only to diseases of the cardiovascular system. The American Cancer Society has estimated that 345,000 persons died of cancer in the United States in 1972. This figure exceeded 452,000 in 1984. In fact, the death rate from cancer rose from 100.6 deaths per 100,000 population in 1930 to 171.7 in 1975. However, these figures are not age-adjusted and, as indicated later in this chapter, much of this increase was due to increasing numbers of older (over age 50) people in our population.

Except for cancer of the skin, the most common and also the most curable of human cancers, 75% of all malignancies in humans in the United States occur in only 10 anatomic sites; these are colon and rectum, breast, lung and bronchus, prostate, uterus, lymph organs, bladder, stomach, blood, and pancreas. In the U.S. male, the most common site of cancer (other than skin) is the lung and accounts for 22% of cancers in the 1980s; one-third of all deaths from cancer in males result from neoplasms of the lung. The second most common site of cancer is the prostate, which has an incidence of 18%, but this is only fifth in cause of deaths and accounts for less than 10% of cancer death in the male. In the U.S. female, cancer of the breast accounts for 27% of the cases of neoplasia and one-fifth of the deaths from cancer. In both males and females in the United States, the incidence of cancer of the colon and rectum is approximately 15% of all cancers.

Figure 1.2 shows the age-specific incidence of cancer at frequent sites for males and females, as reported by Cutler and his associates (1974) from the

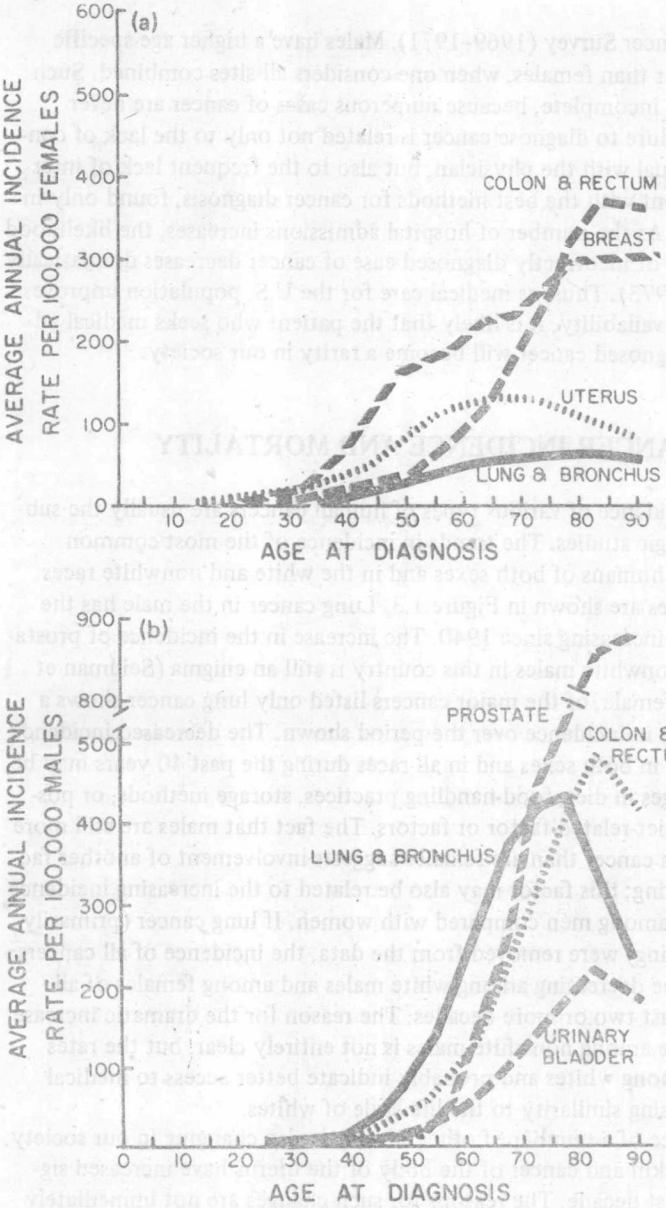


Figure 1.2 Age-specific incidence of cancer at the most frequent sites in the human in 1974 in the United States: (a) females, (b) males. (After Cutler et al., 1974, with permission of the authors and publisher.)

Third National Cancer Survey (1969-1971). Males have a higher age-specific incidence of cancer than females, when one considers all sites combined. Such data, however, are incomplete, because numerous cases of cancer are never diagnosed. The failure to diagnose cancer is related not only to the lack of contact of the individual with the physician, but also to the frequent lack of interaction of the patient with the best methods for cancer diagnosis, found only in modern hospitals. As the number of hospital admissions increases, the likelihood of an undiagnosed or incorrectly diagnosed case of cancer decreases dramatically (cf. Bauer et al., 1973). Thus, as medical care for the U.S. population improves in efficiency and availability, it is likely that the patient who seeks medical advice and has undiagnosed cancer will become a rarity in our society.

TRENDS IN CANCER INCIDENCE AND MORTALITY

Changes in the incidence of various types of human cancers are usually the subject of epidemiologic studies. The trends in incidence of the most common types of cancer in humans of both sexes and in the white and nonwhite races in the United States are shown in Figure 1.3. Lung cancer in the male has the highest incidence, increasing since 1940. The increase in the incidence of prostatic cancer in the nonwhite males in this country is still an enigma (Seidman et al., 1976). In the female, of the major cancers listed only lung cancer shows a significant increase in incidence over the period shown. The decreased incidence of stomach cancer in both sexes and in all races during the past 40 years may be the result of changes in diet, food-handling practices, storage methods, or possibly some other diet-related factor or factors. The fact that males are still more subject to stomach cancer than are females suggests involvement of another factor, possibly smoking; this factor may also be related to the increasing incidence of bladder cancer among men compared with women. If lung cancer (primarily the result of smoking) were removed from the data, the incidence of all cancers combined would be decreasing among white males and among females of all races during the past two or more decades. The reason for the dramatic increase in cancer incidence among nonwhite males is not entirely clear, but the rates approach those among whites and probably indicate better access to medical care and an increasing similarity to the life-style of whites.

The incidence of a number of other cancers is also changing in our society. Melanoma of the skin and cancer of the body of the uterus have increased significantly in the last decade. The reasons for such changes are not immediately apparent.

On a world-wide scale, the incidence of cancer is somewhat different from that in the United States. Table 1.1 lists the ten most common cancers (except skin) on the basis of recent information obtained by the International Agency