FUNDAMENTALS OF ONCOLOGY

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McArdle Laboratory for Cancer Research
University of Wisconsin Medical School
Madison, Wisconsin

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Preface

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 specifically 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 Riegel, Bill Sugden, Howard 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 epilog, and to Mr. John L. Shane, whose artistic skill produced the drawings of the figures.

McArdle Laboratory for Cancer Research
University of Wisconsin Medical School
Madison, Wisconsin

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Cancer: Yesterday and Today

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

Cancer as a disease presents interesting paradoxes. While the layman looks upon it as perhaps the ultimate horror of all diseases ending in painful, suffering death, the physician views cancer as another general type of disease such as inflammation, trauma, toxic or degenerative disease. Many consider cancer as a multitude of different diseases with an underlying biological kinship. To the experimentalist working in cancer research, the cancer cell results from one or more derangements in the biological chemistry of a normal cell.

In 1970 a special panel of consultants called together by the U.S. Senate submitted a report on "A National Program for the Conquest of Cancer." Although the United States was not the first country to make the conquest of cancer a national effort, the financial backing requested and ultimately passed by the executive and legislative branches of government, respectively, gave 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. This committee of consultants generated a report which at that time 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 in fact the primary health concern of the people of the United States. In a number of polls, approximately two-thirds of those questioned admitted fearing cancer more than any other diesease. Of 200 million Americans living in 1970, 50 million were destined to develop cancer at the then present rate of incidence, and some 34 million would die of the disease. 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. Since 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 pointed out that in 1969 the budget of this country, calculated on a per capita basis, enlisted $410 for national defense; $125 for the war in Viet Nam; $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 all six years of the Viet Nam war up to that time, 5-1/2 times the number of people killed in automobile accidents in

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

that year, and greater than the number of American servicemen killed in battle in all four years of World War II. Literally billions of dollars are lost each year to this nation's economy as a direct result of the ravages of this disease.

This report also emphasized certain other points in relation to this disease. Data demonstrated that the incidence of cancer is increasing, partly because of the fact that the age of our citizenry is increasing. Clearly, cancer strikes more frequently in the older age groups. However, a primary cause for the increased incidence is the sharp increase in lung cancer, probably attributable to a small extent to air pollution in certain environments in our country, but especially to the "self-pollution" of cigarette smoking. The panel estimated that if Americans stopped smoking cigarettes, this alone would eliminate 15% of all cancer deaths in this country within several decades.

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 case in five. Today, approximately one in three is cured, and the panel estimated that this could be improved to almost one in two simply by better application of the knowledge which exists today. 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.* 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 the human patient, and in one papyrus a glyph clearly refers to a clinical tumor (Figure 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

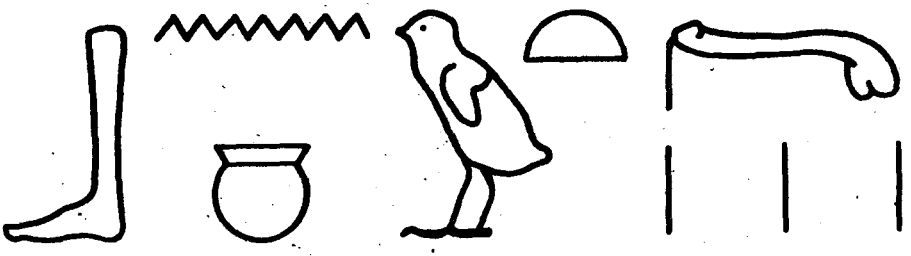

Figure 1: The symbol for "tumor' referring to the surgical treatment of cancer in the hieroglyphics of the Edwin Smith papyrus dating back to more than 1,600 years B.C. The reader is referred to Breasted's translation of the document for further information.

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. 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 fraction; 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 between a crab and the disease we know today as cancer. Since the latter term is derived from the Latin and carcinoma from the Greek, it is likely that Galen was following in Hippocrates' footsteps.

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 1,600 years. Bichat 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. Some 17 years later, Johannes Müller 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 this time little was known about cell division, and Pasteur and

others had not yet clearly demonstrated the doctrine *omnis cellula e cellula*, i.e., every cell from a cell.

A student of Müller, Rudolf Virchow, 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 relationship 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 supported the latter concept, as did Julius Cohnheim at a later period when, in 1877, he 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," although Laënnec recognized 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 (vide supra) 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.*"

Another major advance during this period was the demonstration by Waldeyer that metastases were the result of cell emboli. In addition, he was able to show that cells infiltrated from primary cancers into 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 knowledge. 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. The history of studies on the etiology of cancer is fascinating and is dealt with briefly later as part of our discussion of carcinogenesis.

Obviously the experimentalist needs a hypothesis from which he or she formulates and performs experimental investigations. During the nineteenth century, many hypotheses of the origin and development of cancer were presented. In general, however, one may place these into three categories, as follows:

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

Into the first of these could be placed what little was known at that time of the effects of chemical agents, mostly crude, and of radiation in the genesis of cancer. The relationships 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 these are present from birth, and an extremely tiny percentage of such structures will become cancerous. Many neoplasms of embryonic tissue appearance, such as the teratoma occurring in the adult, would also tend to support this type of hypothesis.

In view of the rapid advances made in our understanding of infectious disease during the last century by Pasteur and numerous others, it is quite understandable that physicians and scientists searched for an infectious origin of cancer. Several reports occurred at the end of the nineteenth century, including that of Doyen, who described a bacterium, *Micrococcus neoformans*, which he isolated from several neoplasms and believed to be the cause of all types of cancer. As it turned out, this organism was merely a common staphylococcus. It was not until the twentieth century that this hypothesis became scientifically sound. Even in this century, more than 50 years were to pass before proper scientific recognition was given to the parasitic hypothesis.

Cancer: Today

Cancer has risen from the eighth most common cause of death in the United States in 1900 to the second most common cause of death in 1972, second only to disease of the cardiovascular system. The American Cancer Society has estimated that 345,000 persons died of cancer in the United States in 1972. In all likelihood, this figure will exceed 350,000 in 1978. Except for cancer of the skin, which is the most common and also the most curable of human cancers, 75% of all malignancies in human beings 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 male the most common site of cancer (other than skin) is the lung and accounts for 22% of cancer in the 1970s; one-third of all deaths from cancer in males result from neoplasms of the lung. The second most common site of incidence is the prostate, but this is only fifth in cause of death and accounts for less than 10% of cancer deaths in the male. In the female, cancer of the breast accounts for 27% of the cases of neoplasia and one-fifth of the deaths from this disease. If males and females are considered together, then the leading types of neoplasms (still excepting skin), accounting for approximately 15% of all cancers, are those of the colon and rectum, followed by breast and lung, with an incidence of 13.6% and 13.3%, respectively.

The age-specific incidence of cancer, when one considers all sites combined, shows that males have a higher incidence than females. The age-specific incidence of frequent sites for males and females is seen in Figure 2. These data are taken from the work of Cutler and his associates. Unfortunately, the data seen in Figure 2 do not tell the whole story. Physicians have been aware for many years that numerous cases of cancer are never diagnosed. While some have argued that the marked increase in the incidence of cancer reported in the human is due to better methods of diagnosis (vide infra), this cannot account for all of the increase seen in this disease. The failure to diagnose cancer is not only related to the lack of contact of the individual with the physician but also to the frequency of the 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. Thus, as medical care for the U.S. population increases in its efficiency and availability, it is quite likely that the patient who seeks medical advice and yet 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 neoplasms are really the subject of epidemiologic studies. One of the best known examples in this country is the decreasing incidence of cancer of the stomach, in contrast to an increasing incidence of cancer of the lung over the past 25 years. The survival rates of patients with cancer have been increasing, but with a rather interesting pattern. As can be seen in Table 1, the increase in survival rate for many neoplasms was quite significant between the 1940s and the 1950s.

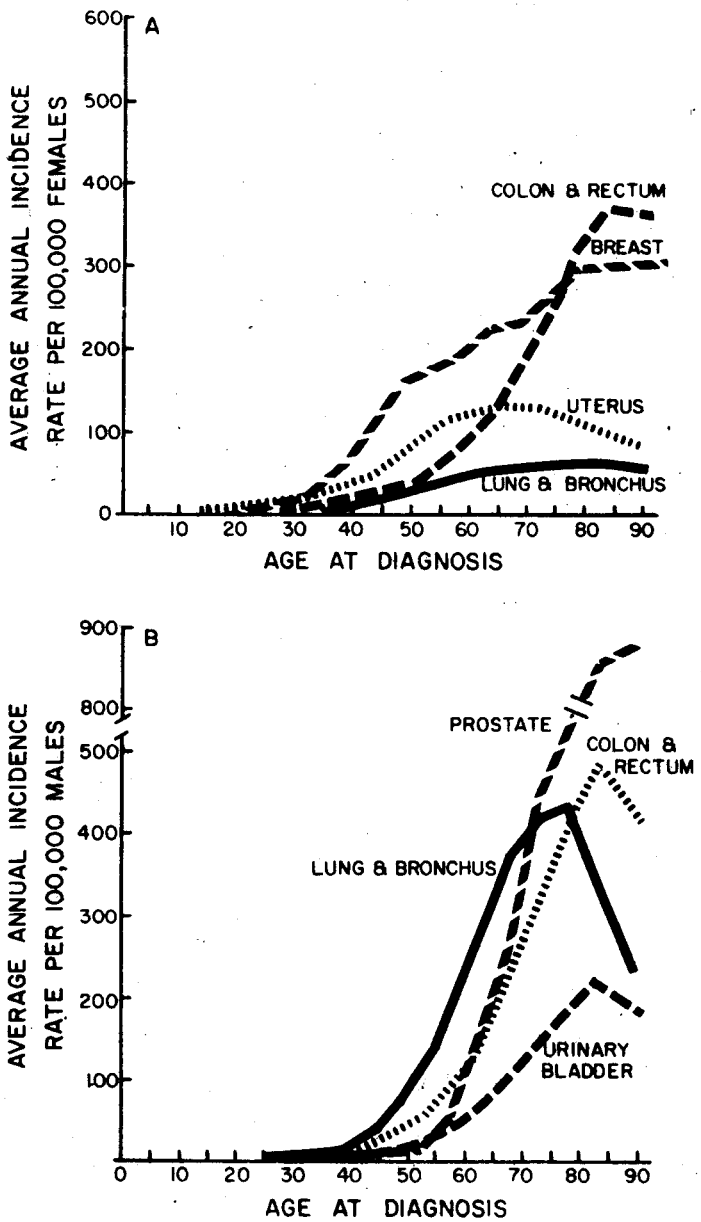

Figure 2: Age-specific incidence of cancer at the most frequent sites in the human. A, females; B, males (After Cutler.)

Table 1. Trend in 5-Year Survival Rates for Cancers[a] Diagnosed in 1940-1969

Primary site	% of all Cancers[b]	5-year relative survival rates (%)[c] according to calendar period of diagnosis			
		1940-49	1950-59	1960-64	1965-69
Breast (females)[d]	13.9	53	60	62	64
Lung	13.1	4	8	9	9
Colon	10.4	32	44	44	45
Prostate[d]	7.9	37	47	52	56
Rectum	4.6	29	40	37	41
Bladder[d]	4.6	42	55	56	60
Corpus[d]	3.8	61	71	73	74
Stomach	3.3	9	12	12	12
Pancreas	3.1	1	1	1	2
Cervix (invasive)	2.7	47	59	57	56
Ovary	2.6	25	29	33	32
Kidney[d]	1.8	26	34	36	41
Brain	1.6	24	25	24	29
Melanoma (skin)[d]	1.5	41	56	62	67
Larynx[d]	1.4	41	56	54	61
Thyroid[d]	1.3	64	80	83	84
Gall bladder	1.0	3	6	8	8
Pharynx	1.0	18	22	24	23
Chronic leukemia[d]	1.4	15	23	27	30
Acute leukemia[d]	1.2	0	1	2	3
Hodgkin's disease	1.1	25	34	42	54
Multiple myeloma[d]	1.1	7	7	11	16
Lymphosarcoma[d]	1.0	23	28	31	32
Leukemia in children:					
All types[d]	e	0	1	4	6
Acute lymphocytic[d]	e	0	0	4	6

[a]Data for white patients only. Data on nonmelanotic skin cancer are not included in this table.

[b]Based on Third National Cancer Survey, 1969-1971.

[c]The relative survival rate adjusts for normal mortality expectation. Thus, meaningful comparisons can be made of survival among patient groups that differ in race, sex, and age.

[d]Continued improvement in survival through 1965-1969.

[e]Included in percentages given above [From Cutler et al., *New Eng. J. Med.* 293 (1975): 122.]

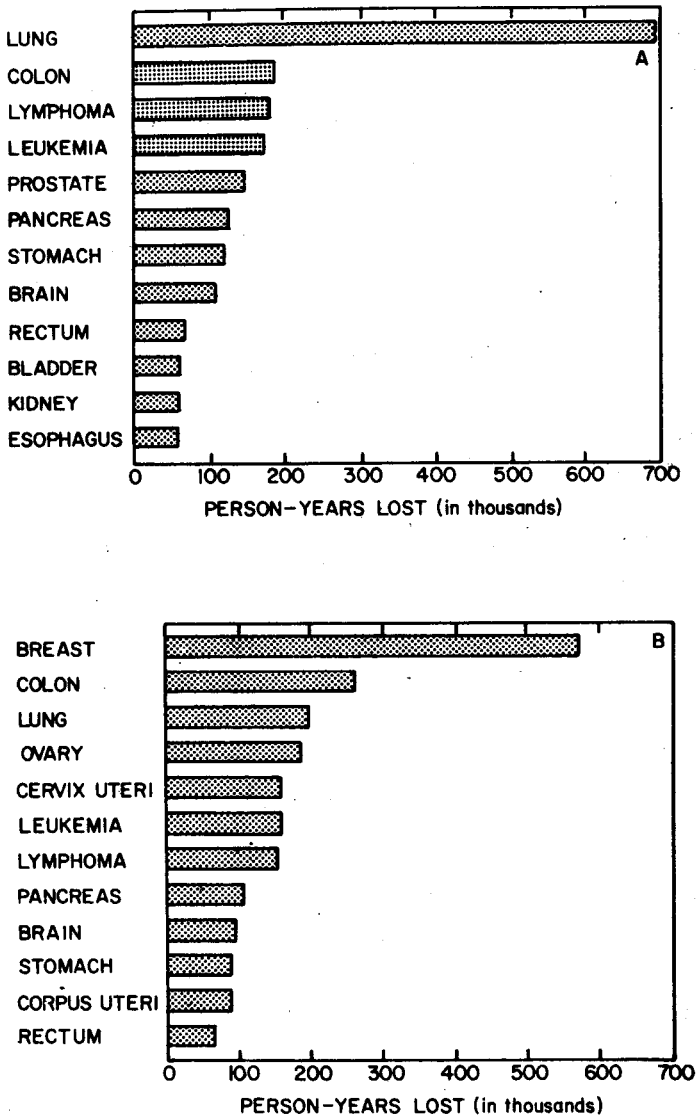

Figure 3: Total and productive years of life lost due to cancer mortality in 1968. A, person-years lost from the leading types of cancer in males; B, person-years lost from the leading types of cancer in females; C, work-years lost from the leading types of cancer in males; D, work-years lost from the leading types of cancer in females. (After Murray and Axtell.)