Cancer

DIAGNOSIS, TREATMENT, and PROGNOSIS

Lauren V. Ackerman, M.D. Juan A. del Regato, M.D.

FOURTH EDITION

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Lauren V. Ackerman, M.D.

Professor of Surgical Pathology and Pathology, Washington University School of Medicine, St. Louis, Mo.; Surgical Pathologist in Chief to Barnes and Affiliated Hospitals and St. Louis Children's Hospital, St. Louis, Mo.; Consultant, Ellis Fischel State Cancer Hospital, Columbia, Mo.; Consultant, Armed Forces Institute of Pathology; Visiting Professor of Surgical Pathology, University of Witwatersrand, Johannesburg, R.S.A. (1969)

Juan A. del Regato, M.D.

Director, Penrose Cancer Hospital, Colorado Springs, Colo.; Clinical Professor of Radiology, University of Colorado School of Medicine; Member, National Advisory Cancer Council; Member, Board of Chancellors, American College of Radiology; Member, Advisory Commission on Biology and Medicine, Puerto Rico Nuclear Center; Member, Committee on the Genito-Urinary System, National Academy of Science–National Research Council

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To
ELIZABETH AND INEZ

Preface

Our purpose in writing this book has been to provide a text that will bring general information to the student, to the general practitioner, and to those specialists involved in the diagnosis and treatment of malignant tumors. Some articles in the current literature, often devoted to treatment, assume that the correct diagnosis has been established and may not even mention the clinical evolution or differential diagnosis. Others, devoted to histopathology, may give no information on incidence or prognosis. Our intention is to present an integrated view of all of these aspects and to point the way toward a more thorough basis of knowledge of malignant neoplasms.

Chapters 1 through 5 are devoted to subjects of general interest. *Dr. Michael Shimkin,* Professor of Community Medicine and Oncology, School of Medicine, University of California at San Diego, has written the chapter on *cancer research* for all four editions. *Dr. Harvey R. Butcher, Jr.,* Professor of Surgery, Washington University School of Medicine, has contributed the chapter on *surgery of cancer* to this edition and to the previous edition. The introductory chapter and the chapters on *pathology of cancer* and *radiotherapy of cancer,* written by us, complete this portion of the book.

Chapters 6 through 18 are organized according to systems or organs and are subdivided as necessary. Use of the word *cancer* in the chapter titles indicates that malignant tumors of different origin are included; the term *carcinoma* is used when only malignant epithelial neoplasms are considered, and the rarer tumors of the same area are included in the discussion on differential diagnosis; the word *tumor* is used whenever the frequency or the seriousness of the benign tumors, the difficulties of their differential diagnosis, or the importance of their treatment justifies a joint consideration.

Chapters 19 and 20 are devoted to *Hodgkin's disease* and *leukemia,* respectively, since these two important manifestations of neoplasia justify separate consideration.

The length of some chapters is neither commensurate with the importance of the subject nor with the incidence of the tumor under consideration. This disparity has been deliberate, for we have been guided rather by the desirability of information in certain rare subjects and by the necessity of greater knowledge on some aspects of the more curable forms of cancer. Important recent developments have also received priority on space.

The subject matter in Chapters 6 through 20 is presented under the following headings: anatomy, epidemiology, pathology, clinical evolution, diagnosis, treatment, and prognosis.

Under *anatomy* is included a short description of the relevant structures, with emphasis on details pertinent to the development of cancer, its symptoms and treatment. Also, a detailed discussion of the *lymphatics* of the organ or region is featured because of the unquestionable importance of these vessels in the understanding of the spread and the treatment of malignant tumors.

Under *epidemiology* is gathered whatever useful information is available concerning incidence, ethnic or racial predilections, sex and age ratios, and known

mat to conserve space and thus preserve the work in one volume.

Thousands of patients everywhere are depending on the judgment, knowledge, and skill of their various physicians. Although some forms of cancer remain incurable, there is no room for temporizing guesswork, amateurish approaches, or defeatist attitudes. Success depends entirely on intelligent understanding, skillful treatment, and a hopeful, compassionate attitude.

Contents

Chapter 1

Introduction

Cancer is a generic term used for a large number and wide variety of malignant neoplasms, possibly related to as many different causes, that arise from any of the tissues of the human body (as well as from tissues of other animals) and result in deleterious effects on the host due to their invasive and metastasizing character. Since, in this book and in other medical publications on cancer, the words incidence, prevalence, occurrence, distribution, frequency, and mortality are used, it is important that their meanings be understood.

Incidence expresses the number of new cases diagnosed during one year in some well-defined population. The word incidence is incorrectly used unless it is related to total population. *Incidence rate* is the ratio of incidence to population, usually expressed as the number of new cases per 100,000 persons. Since some malignant tumors occur only in men or in women, their incidence may be expressed in terms of the total male or female population (i.e., as *sex-specific incidence rates*). Since some forms of cancer have a predominance for subjects within a given age group, their frequency may be given in terms of *age-specific rates* to conform to the actual population within such limits.

Prevalence is the number of cases (old or new) known to have been present during a given year and may be expressed as a *prevalence rate* per 100,000 population.

Often what is expressed, without relation to total population or time, is the *frequency* of cases of cancer in a community. Reports of hospital registration of cases and their classification according to organ, histopathology, age, sex, etc. is not incidence but frequency. *Relative frequency* is the percentage of cases of one form of malignant tumor in reference to all cases of cancer.

Mortality rates are expressed as number of patients dead of cancer within one year per 100,000 population.

Incidence rates, prevalence rates, and mortality rates are often calculated for the purpose of comparisons among different areas or populations. If the populations vary markedly in age or sex composition, it may be difficult to interpret any difference in rates unless they are *adjusted* to a single common population. The most usual standard for these conversions in the United States is the composition of the population in the census of 1950.

The *total incidence* of cancer in the different countries of the world may vary considerably for various reasons. One important variant influencing incidence is the average life span of the individuals in a nation, for as the public health improves and life expectancy is increased, cancer becomes a greater problem. The *relative incidence* of certain forms of cancer may vary from one country to the other for specific reasons of race, culture, habits, varied environmental differences, etc. which may hold a clue as to the cause or causes that bring them about (Dunham and Bailar[12]).

Some characteristically high incidences of given malignant tumors can be uncovered only if demographic and diagnostic facilities and information are available for proper evaluation (Marcial[37, 38]). Mortality rates do not give a correct idea of these differences nor of the relative frequency of all tumors. For one thing, mortality statistics disregard the relative curability of the various malignant tumors which differs from one area to another. For another, the diagnosis on death certificates is often based on clinical assumption and seldom verified histologically. In a study of 1,000 autopsies of cases clinically diagnosed as cancer, Willis[66] found that 310 were misdiagnosed as to point of origin and that no cancer was present in fifty-seven. The proportion of errors was greater for deep-seated primary tumors of the stomach, kidney, pancreas, etc. The true

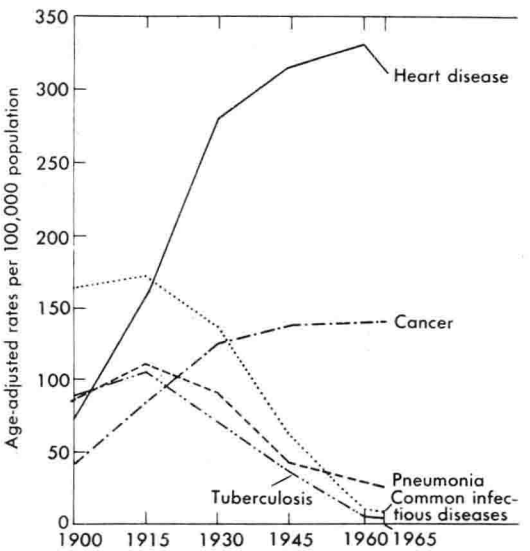

Fig. 1. Age-adjusted mortality rates for selected causes of death in United States in twentieth century. (Courtesy Dr. John C. Bailar, III, and Staff of Demography Section, Biometry Branch, National Cancer Institute.)

trend of cancer mortality can only be evaluated in the light of representative samples of cancer incidence (Levin[33]; Levin et al.[34]).

In 1900 there were in the United States 13 million persons over 45 years of age. By 1948 there were 39 million, in 1958 some 50 million, and in 1968 59 million. Since cancer is prevalent among aged individuals, the number of cases of cancer has increased by virtue of this increase in the relatively aged population alone. More than half of the cancer risk in men is due to cancer of the skin, lung, prostate, and intestine, whereas more than half of the risk in women is due to cancer of the breast, cervix, skin, and intestines. During a lifetime, 1 in every 5 men and 1 in every 4 women may be expected to develop cancer (Goldberg et al.[19]). The 1948-1949 survey of the National Cancer Institute revealed a cancer incidence rate of 40 per 100,000 individuals under 25 years of age, 475 per 100,000 for those under the age of 50 years, and 1900 per 100,000 for those under 75 years of age.

In 1966, with a total population of nearly 200 million in the United States, the estimated numbers of new cases of cancer and of cancer deaths, for all sites, were 600,000 and 300,000, respectively (National Impact of Cancer[43]). The outstanding recent changes observed are as follows:

1 A considerable decrease in the incidence of cancer of the stomach
2 A marked decrease in the incidence of invasive carcinoma of the cervix
3 A progressive increase in the incidence of acute leukemia
4 A remarkable continued increase in the incidence of carcinoma of the bronchus (Foote et al.[16])

Cancer of the colon and rectum, in both sexes, leads in incidence. Cancer of the breast and uterus remain the most frequent in women and cancer of the lung and prostate are the most frequent in men. The gap between the greater probability of cancer in women than in men is closing due mainly to the persistent greater incidence of cancer of the lung in men. A study of cancer mortality rates of immigrants in the United States shows an excess mortality for cancer of the esophagus and stomach (Haenszel[23, 24]).

The mistaken concept that cancer is the curse that accompanies civilization has been dispelled by the increasing evidence that the incidence of certain forms of cancer is remarkably elevated in underdeveloped populations. Significant differences in the incidence of some malignant tumors are evident, but it is not explained whether they are due to racial or environmental differences in the various countries. Considering their relationship to environment, Higginson[27] proposes that the studied forms of cancer be divided into:

1 Cultural (oral cavity—betel nut)
2 Industrial (bladder—dyes)
3 Idiopathic (marked geographic variations—no evident etiology)
4 Miscellaneous (mostly occurring in children—no geographic variations)

The outstanding observed high incidences are cancer of the *nasopharynx* in China, primary cancer of the *liver* in the South African Bantu, cancer of the *stomach* in Japan, cancer of the *esophagus* in Puerto Rico, certain areas of South Africa, and Japan, and cancer of the *lung, colon, rectum,* and *endometrium* in the United States, United Kingdom, and Denmark (Fig. 4).

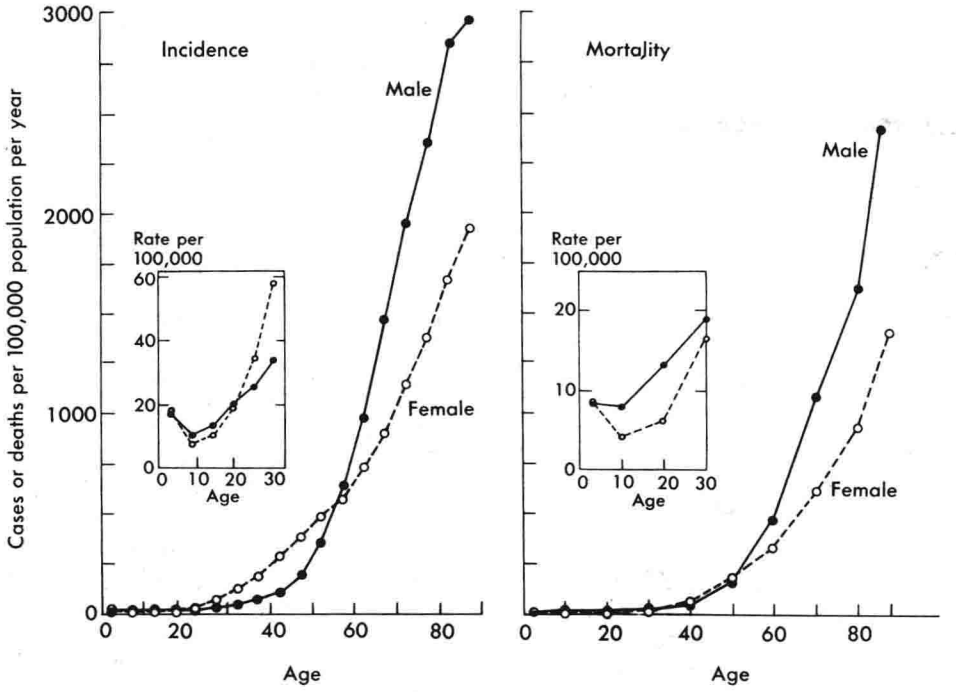

Fig. 2. Cancer incidence and mortality rates for males and females according to age. (Courtesy Dr. John C. Bailar, III, and Staff of Demography Section, Biometry Branch, National Cancer Institute.)

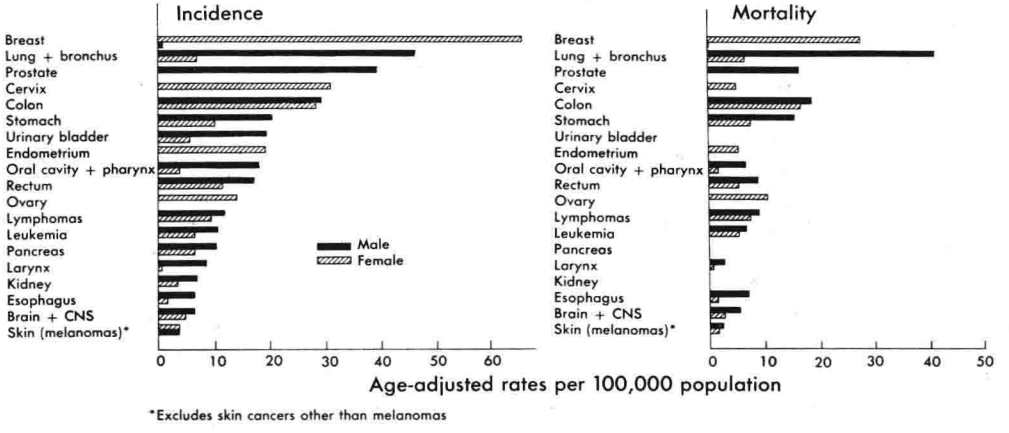

Fig. 3. Age-adjusted cancer incidence and mortality rates for major forms of cancer in United States. (Courtesy Dr. John C. Bailar, III, and Staff of Demography Section, Biometry Branch, National Cancer Institute.)

The distribution of patients with cancer admitted to different hospitals varies with the economic, racial, and age composition of the clientele as well as with the type of institution (Table 1). Hospitals devoted to the treatment of aged, rural, indigent patients show a preponderance of cancer of the skin and lip (Modlin[39]). Urban general hospitals, on the other hand, report greater numbers of cancer of the gastro-

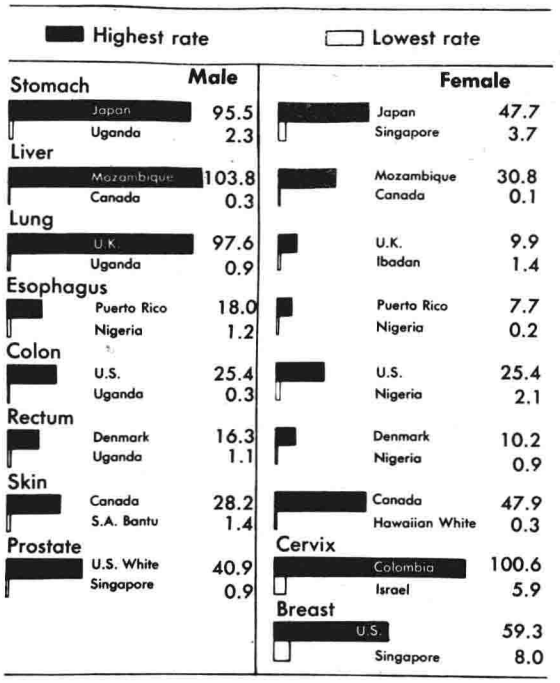

Fig. 4. Highest and lowest observed age-adjusted rates of incidence for selected cancer sites. Wide differences considered to indicate variations in exposure to environmental agents. (From Higginson, John: Annual Report, International Agency for Research on Cancer, World Health Organization, 1968.)

intestinal tract, with autopsy series revealing predominantly deep-seated or rare forms of cancer which motivated postmortem examination (Saxton et al.[54]).

A knowledge of the relatively greater or lesser incidence of the different forms of cancer in the different age groups is important in clinical practice (Fig. 5). Leukemia, and tumors of the eye, brain, bone, and kidney predominate in patients of both sexes under 15 years of age, whereas cancer of the colon and rectum, cancer of the lung and prostate in men, and cancer of the breast and uterus in women show a relatively higher incidence among those 65 years of age or older. The high cancer death rate in children (Fig. 6) relative to other causes is worthy of note (Paterson[46]). Considering the major forms of cancer, the present yield of diagnosis, the results of treatments, and the mortality, one might estimate arbitrarily the size of the educational and research problems (Table 2) as suggested by Steiner[59].

Diagnosis

The results of the treatment of certain forms of cancer are, to some extent, influenced by the time interval that elapses

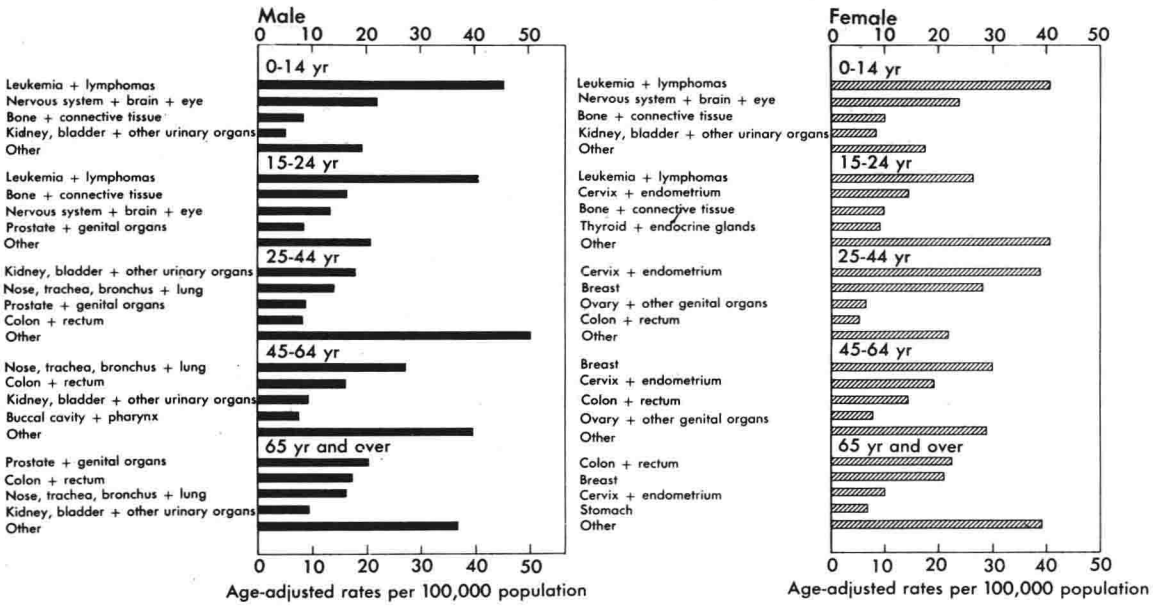

Fig. 5. Cancer incidence rates in broad age groups. (Courtesy Dr. John C. Bailar, III, and Staff of Demography Section, Biometry Branch, National Cancer Institute.)

between the genesis of the lesion and its diagnosis, and the patient is too often blamed for any delay. Large amounts of money have been expended and considerable attention given to the education of the laity as to the early signs and symptoms of cancer in an effort to get them to seek attention promptly. Such education of the public, which should be extended to high school youngsters, is limited by the educational level of population groups and can improve only with the betterment of

Table 1. Comparison of most common forms of cancer reported in patients admitted to a rural cancer hospital and observed at autopsy in a city hospital

*Ellis Fischel State Cancer Hospital Columbia, Mo.**			*St. Louis City Hospital St. Louis, Mo.†*	
% of all cases of cancer	*Organ*	*Rank*	*Organ*	*% of cancer autopsies*
36	Skin	1	Large bowel	20
13	Breast	2	Lung	15
12	Cervix	3	Stomach	13
7	Lips	4	Prostate	9
6	Large bowel	5	Cervix	8
2.3	Endometrium	6	Breast	7
1.9	Stomach	7	Bladder	6.8
1.8	Melanocarcinoma	8	Esophagus	6.5
1.6	Prostate	9	Pancreas	6.2
1.5	Ovary	10	Brain	6.1

*Data from Modlin, J. J.: Five-year results of treatment, Ellis Fischel State Cancer Hospital, Proceedings of the Thirty-fourth Annual Clinical Congress, American College of Surgeons, pp. 38-41, 1948.
†Data from Saxton, J. A., Jr., Handler, F. P., and Bauer, J.: Cancer and ageing, Arch. Path. (Chicago) **50**:813-827, 1950.

Table 2. Comparison of present control with educational and research problems in cancer

Rank	*Primary site of cancer*	*Number of deaths*	*% of cancer deaths*	*Five-year relative survival rate (%)*	*Estimates of*	
					Size of educational problem (%)	*Size of research problem (%)*
	All malignant neoplasms	303,736	100.0	—	—	—
1	Lung and bronchus	51,348	16.9	8	62	30
2	Colon and rectum	43,474	14.3	45	10	45
3	Breast	27,533	9.1	61	19	20
4	Stomach	17,623	5.8	13	7	80
5	Pancreas	16,360	5.4	1	0	99
6	Prostate	15,941	5.2	49	31	20
7	Lymphatic system	15,802	5.2	30	35	35
8	Leukemia	14,012	4.6	20	5	75
9	Uterus (cervix and endometrium)	13,396	4.4	65	25	10
10	Ovary	9,041	3.0	30	5	65
11	Urinary bladder	8,136	2.7	57	18	25
12	Brain	5,881	1.9	25	15	60
13	Kidney	5,841	1.9	36	14	50
14	Esophagus	5,505	1.8	1	0	99
15	Liver	5,261	1.7	1	0	99
16	Skin (including melanoma)	4,560	1.5	98	1	1
17	Gallbladder and ducts	4,471	1.5	7	0	93
18	Pharynx	2,797	0.9	25	25	50
19	Larynx	2,623	0.9	57	23	20
20	Bone	1,792	0.6	35	15	50
21	Tongue	1,629	0.5	33	17	50
22	Connective tissue	1,318	0.4	51	10	39
23	Thyroid gland	1,008	0.3	78	12	10
	All other sites	28,384	9.3	—	—	—

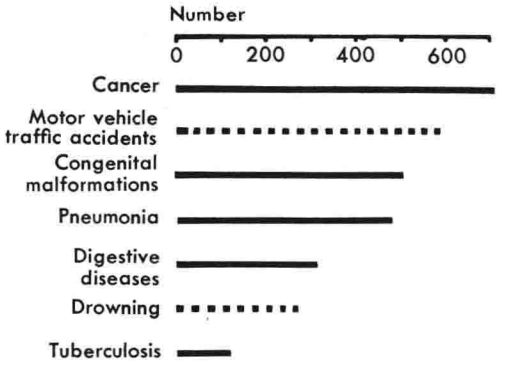

Fig. 6. Cancer in relation to certain other causes of death in children 1 to 14 years of age, England and Wales, 1955. (From Paterson, E.: Malignant tumours of childhood, J. Fac. Radiol. 9:170-174, 1958.)

the standards of general education and general medical care. The American Cancer Society has made a worthwhile effort to make the public conscious of the importance of early diagnosis.

Considerable betterment may be derived from implementation of what we already know: "The vast majority of the cancer patients of today are far from receiving the benefits of knowledge, facilities and skills which have been available for decades; they have benefitted only a few. From early diagnosis to successful treatment the cancer patient is subject to a venturous course. The varied hurdles include: wishful thinking (to which physicians are not immune), geography, luck, misinformation (lay and professional), organization, luck, facilities, skills and a great deal of luck. In short, *too few make it where many could.* In practically every instance of failure there are several physicians, with varied skills, who did their diagnostic and therapeutic best: their very best was not equal to the needs of the case."*

It has long been recognized that one of the best means of obtaining an early diagnosis in certain forms of cancer is the periodic physical examination of symptomless patients (Regaud[51]). These periodic screening examinations, however, must be performed by examiners well trained in the diagnosis of early cancer. Otherwise, they may convey a sense of false security to the patient. L'Esperance, McFarlane, Schram, and others were pioneers in developing a series of cancer screening clinics in the United States, the function of which was the examination of apparently healthy individuals in an attempt to detect cancer in its early stages. By 1950, there were 251 cancer screening centers in the United States. Levin[33] estimated that only in individuals past 55 years of age will these examinations be capable of yielding more than five cases of cancer for every 1000 individuals examined, because 75% of all cancer in men and 60% of all cancer in women occur past this age. Such "yield" may be considered worthwhile from a public health standpoint, but the cost of finding a case of cancer has been estimated by Newell[44] to be between $7,000 and $10,000.

The approach of cancer detection centers to the problem of early diagnosis has definite shortcomings. The time, personnel, effort, and facilities required make the attempt necessarily limited to a fraction of the population. In some centers, registrants have been obliged to wait from six to twelve months for an examination. Yet, such examinations should be repeated at least once annually if they are to render full usefulness. Further, such centers must, of necessity, undertake to advise patients when diseases other than cancer are discovered. Also, after centers have been in operation for some time, an ever-increasing number of patients are seen who have had a diagnosis of cancer but seek a confirmation of the diagnosis (Garland[17]). The increasing demands make the undertaking limitless, and the activities must be curtailed.

If a great number of individuals are to receive periodic examinations for the detection of symptomless cancer, the procedure should be reversed, with the effort and expense directed toward the aim of making *every doctor's office a cancer detection center.* We endorse MacDonald's statement:

"Detection centers as currently operated contribute little directly to education, lay or professional, and render a minimum service because of the small number of ex-

*From del Regato, J. A.: The community cancer hospital (1969 presidential address, American Radium Society), Amer. J. Roentgen. 108:3-8, 1970.

aminees and their failure to continue periodic examinations."*

Little is accomplished by the early diagnosis of cancer if the proper therapeutic skill and facilities are not made available to the patient. The patients with cancer discovered in "cancer detection" centers are, as a rule, returned to their family physicians, and a large proportion of them are not subsequently followed. Under these circumstances, the very purpose of early diagnosis, the institution of adequate treatment, fails to culminate the effort. This paradox leaves little room for satisfaction, for a cancer that has been diagnosed early is as hopeless in unskilled hands as an advanced lesion. It would therefore seem more logical to devote more attention to the education of the practicing physician. Also, it may be justly considered whether the effort and expense cannot be put to better service in increasing and sponsoring facilities for the training of specialists (tumor pathologists, radiotherapists, and surgeons) on whose skills the therapeutic results will greatly depend. Such facilities provide the best means for improving medical cancer knowledge which unquestionably results in earlier diagnosis and treatment.

Treatment

If the prognosis of a patient with cancer depends in part upon the early diagnosis, the perfection of the treatment, whether it be surgical or radiotherapeutic, is decisive for cure or for death. Surgeons, radiotherapists, or medical oncologists who undertake to treat patients with cancer assume a heavy responsibility, for the life of the patient may be at stake. The constant thought of any physician should be to seek what is best for his patient rather than to impose on him the limitations of his own medical specialty.

It is imperative that the fundamental choice of method and execution of treatment of patients with cancer be entrusted only to those who are adequately trained and qualified. With the advent of radiotherapeutic methods in the beginning of this century, it became more and more clear that a concerted effort was necessary in the fight against this disease and that such effort was better coordinated within special institutions. The Radium Institute of the University of Paris, The Radiumhemmet of Stockholm, the Memorial Hospital for Cancer and Allied Diseases in New York, and others made the first efforts toward an appropriate organization of facilities and toward the training of workers in this field. In 1929, a special committee of the American Society for the Control of Cancer (Ewing et al.[15]) reported upon the question of therapeutic cancer centers as follows:

". . . We have been forced to conclude that the treatment of many major forms of cancer can no longer be wisely entrusted to the unattached general physician or surgeon, or to the general hospital as ordinarily equipped, but must be recognized as a specialty requiring special training, equipment and experience in all arms of the service. We feel that the futher development of cancer therapeutics will develop along the lines of concentration, organization and specialization. . . . It is well known that the most conspicuous work in the treatment of cancer has long been accomplished by specialists. . . .

"We recommend, as an ideal well within the possibility of accomplishment, the establishment of a limited number of cancer institutes. They should be located in large cities, be prepared to give the best modern treatment, and offer facilities for research and education in the field of cancer."*

To recognize this triple aim of treatment, research, and education is to recognize that cancer institutions be exceptionally well staffed. It would indeed be dangerous to entrust these responsibilities to amateur specialists or to those who have only an incidental or sentimental interest in the disease not only because the results of treatment would suffer considerably, but also because of the unquestionable danger of a spirit of defeat that they would spread among the members of the medical profession. The accumulation of clinical and

*From MacDonald, I. Cancer detection, Arizona Med. **10**:1-10, 1953.

*From Ewing, J., Greenough, R. B., and Gerster, J. C. A.: The medical service available for cancer patients in the United States, J.A.M.A. **93**:165-169, 1929.

pathologic data in such institutions creates the background for training additional personnel. Thus the institutions fulfill not only a therapeutic service, but also the much broader service of educating and training specialists upon which the most immediate hope of cancer control depends.

In establishing a cancer institute or hospital, the most important step is choosing the staff. "The staff of the institute must be chosen with the realization that upon this selection alone depends the success or failure of the project; that neither the building nor the size of the endowment but the background, training, experience, spirit, imagination and idealism of the leaders and their associates will be the determining factors.

"The growth of the institute must be controlled and limited solely by its scientific contributions and accomplishments."*

Statewide cancer control campaigns usually include the establishment of a series of small centers for diagnosis and treatment strategically placed throughout the territory. Although it is desirable to bring the diagnostic centers closer to the patients, a dissemination of therapeutic facilities requires equal dissemination of capable personnel that is not generally available. If such centers are created, they should be planned for the purpose of diagnosis and screening of patients and to assist in the posttherapeutic follow-up. At any rate, their creation should never be contemplated in the absence, or to the detriment, of a central institution. In an initial stage of cancer control it is preferable to finance the transportation of indigent patients from their homes to the therapeutic center rather than to create multiple small centers where chances of a permanent cure will be extremely reduced.

The creation of cancer hospitals anywhere, by private institutions or by the state, should not be undertaken without securing the support and wholehearted cooperation of the state medical society. Members of the medical profession have become appreciative of these cancer institutions, and experience shows their growing support for them.

*From Cutler, M.: Cancer, Illinois Med. J. **71**: 413-419, 1937.

In the United States, the progressive dispersion of medical facilities has limited the development of large full-time staff cancer institutions. Moreover, the work of full-time cancer hospitals must be limited, for the most part, to the indigent population, which constitutes a small part of the cancer problem. *Open-staff cancer hospitals*, working in conjunction and sharing facilities with a general hospital, are a practical answer (Regato[50]). They will preserve the private practice of medicine while concentrating the necessary surgical, pathologic, and readiotherapeutic skills and facilitating the highly needed training of young physicians and continued postgraduate education of the practicing staff. The economics of such small-sized cancer hospitals are not prohibitive. Well-trained specialists participate in the work rendered and the education of residents in training, thus sharing in the work and in the credit of the institution, without losing their individuality and freedom of practice. The institution makes available to the medical community a measure of full-time skills in diagnosis, treatment, and follow-ups, as well as teaching and research facilities, which reinforce the strength of the participating staff.

In 1930 the Board of Regents of the American College of Surgeons,[2] on the advice of its Committee on the Treatment of Malignant Diseases, announced a new policy. Cancer institutes "require very considerable endowments or such generous annual appropriations as can be obtained usually only from the state or national government. They are undoubtedly the most effective method of dealing with the cancer problem but their cost is such that their number will inevitably be somewhat restricted. . . . Where funds sufficient for the maintenance of cancer institutes, research laboratories, or special cancer hospitals are not available, the demand for improved service for cancer cases has resulted in the organization of special cancer clinics in existing general hospitals and of cancer diagnostic clinics in many places in the country in the past few years."* It

*From American College of Surgeons: Organization of service for the diagnosis and treatment of cancer, Surg. Gynec. Obstet. **51**:570-574, 1930; by permission of Surgery, Gynecology & Obstetrics.