VOLUME V

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CLINICAL CANCER

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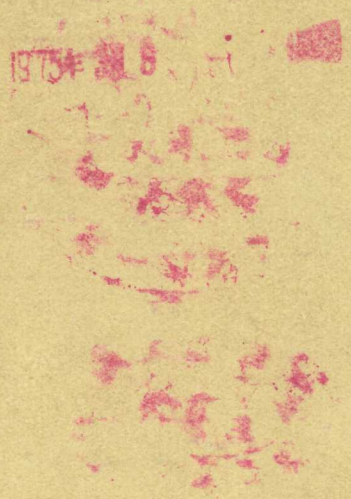
IRVING M. ARIEL, M.D., F.A.C.S.



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Dedicated To

MURRAY M. COPELAND, M.D., D. Sc(Hon)., F.A.C.S.

Dr. Copeland epitomizes a physician who has devoted his entire professional life to the field of clinical cancer since he graduated from Johns Hopkins School of Medicine in 1927.

His extensive trainings in clinical pathology and surgery at the Johns Hopkins Hospital, Mayo Clinic, and the Memorial Hospital for the Treatment of Cancer and Allied Diseases in New York City, prepared him for a lifetime of devotion to clinical oncology.

He served on the faculty of the University of Maryland Medical School and Johns Hopkins School of Medicine from 1937 until 1946. He was appointed Professor of Oncology and Chairman of the Oncology Department, Georgetown University Medical School, Washington, D. C. He became Assistant Director for Education and Professor of Surgery (Oncology) at the University of Texas M.D. Anderson

Hospital and Tumor Institute and later elevated to Associate Director (Education).

He is Past Chairman on a Commission of Cancer, The American College of Surgeons. He is a member of the council of the International Union Against Cancer and Past Vice-President of the James Ewing Society. He is Past President of the American Cancer Society. He was Chairman of the American Joint Committee for Cancer Staging and End Results Reporting. He has served for two terms as a member of the National Advisory Cancer Council on the National Cancer Institute and has further served as Consultant in Oncology at the Clinical Center of the National Cancer Institute. He has chaired the Cancer Control Committee of the National Cancer Institute and served on the Advisory Committee to the Surgeon General of the United States Public Health Service.

Dr. Copeland is a member having served with distinction of many medical and surgical societies and has served on the editorial advisory boards of some of the leading journals dealing with cancer. He is the author of over one hundred and thirty articles and chapters on subjects relating to cancer and has coauthored the classic book, *Tumors of Bone.*

Dr. Copeland is currently President (for International Affairs) the University Cancer Foundation and Professor of Surgery, Department of Surgery, University of Texas, M.D. Anderson Hospital and Tumor Institute; he is Vice-President for North America, Secretary General of the Tenth International Cancer Congress of the International Union Against Cancer which was held in Houston, Texas in May, 1970. He distinguished himself by making this International Cancer Congress one of the finest ever held. Physicians from practically all over the world gathered to exchange knowledge regarding all phases of cancer.

Inasmuch as this series focuses upon progress in clinical cancer, this volume is respectfully dedicated to a physician who is one of the pioneers in devoting his professional lifetime almost exclusively to the diagnosis and treatment of the patients suffering from cancer. He has instituted tremendous investigations into the pathology and classification of numerous tumors, so that a better understanding of the natural history of these oncologic entities would serve to offer earlier diagnosis and better treatment.

The only time in his professional life when he was not associated with cancer was during the Second World War where he served with distinction in the South Pacific and India-Burma Theatre, receiving the Legion of Merit decoration from the Secretary of the Army for his disinguished service.

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Foreword

Progress in Clinical Cancer continues in an evolutionary progressive manner. Inasmuch as oftentimes, "the past is prologued" the volume opens with a chapter on the Challenge of the Biologic Aspects of Cancer of the Breast. A good authority calls upon his many years of exposure to breast cancer and his vast experience to determine which biologic aspects contribute to the natural history of breast cancer. Only with such an understanding can headway be made, and hopefully this prevalent cancer may be eradicated.

A new entity, namely vaginal cancer in young girls noted after their mothers had taken synthetic estrogens during the child-bearing period, focuses upon the fact that the mother's blood may contain carcinogens which will adversely affect the child.

The problem of metastatic cancer from an unknown primary site is one which is indeed perplexing and much light is set upon the clinical management of such situations.

Continued knowledge regarding the role of the lymph nodes and lymphatic vessels in the spread of cancer is mandatory; therefore a better understanding of this phenomenon is needed, so that methods may be developed to prevent such spread. For example, do the lymph nodes exert a local immunologic effect and are they filters of cancer cells? If so, should they be retained during a surgical resection or if they do not exert such an effect, they would be better off removed. These aspects and others are discussed in an excellent chapter by Dr. Karpas, and Dr. Madden.

The early diagnosis of cancer continues to be the hallmark for continued progress so that early treatment may be instituted. The visualization of malignant tumors by radioactive selenomethionine is a provocative chapter.

A comparison between the diagnostic accuracy of liver scans, liver function tests, and liver biopsies as well as the diagnostic accuracy in cancer as determined by postmortem examinations, focuses upon the reliability of some of our present methods of diagnosing properly early cancer.

Chemotherapy continues to make important inroads in the attack against cancer. A special chapter describing results of a combination and sequential chemotherapy for advanced mammary cancer presents light upon the role of cancer chemotherapy for this form of neoplasia. Similarly, immunotherapy continues to make steady advances, and although it does not play a great role in clinical cancer at the present time, the important inroads that this subject is making is impressive and are presented in a superb chapter by Dr. Moore, a pioneer in this field of endeavor.

Increased survival rates are being obtained in the treatment of lymphomas. Two chapters are devoted to certain aspects of treating leukemia and the changing therapeutic approaches to Hodgkin's disease consisting essentially of exploratory laparotomy for staging and splenectomy, as well as more intensive radiation therapy are presented in depth by studies performed at the Yale Medical School.

The volume closes with a Symposium on Ovarian Tumors. This form of cancer, which appears to be increasing in incidence, continues to defy early diagnoses, and the mortality rates continue rather high. Eight chapters dealing with this important

subject are presented from institutions throughout the world. The symposium begins with the treatment of premalignant, and minimally invasive cancers and then presents several unusual types of ovarian tumors, such as those associated with the Peutz-Jeghers syndrome and melanotic ovarian neoplasms. The second-look operation for ovarian carcinoma is also described, as well as the role of radiation therapy including the utilization of radioactive isotopes in the treatment of ovarian cancer. Increased knowledge as presented in this symposium should lead to a better understanding and eventually, better results in the management of cancers arising in the ovaries.

The volume closes with a chapter closely allied to ovarian cancer, namely, cancers arising from the fallopian tube, where a detailed analysis of a large series contributes to an understanding which will result in better management of this form of cancer.

In this volume, 46 esteemed authorities have pooled their knowledge in 21 excellent chapters describing some of the dynamic developments which have occurred in the ever expanding program in clinical cancer.

IRVING M. ARIEL, M.D., F.A.C.S.
New York, New York

Contents

The Challenge of the Biologic Aspects of Cancer of the Breast*

MURRAY M. COPELAND, M.D.

INTRODUCTION

Both mortality data and, more recently, reliable morbidity data have provided us with reasonably accurate information on the frequency of carcinoma of the breast. The crude incidence rate of cancer of the breast in women far exceeds that for any other type found in either sex.[80] Our present statistics on breast cancer are based on findings made in 1947-1948, with a number of less searching studies since then.[25,26,41,42] The statistics available indicate that breast cancer in women is nearly twice the rate of the next most common malignant tumor found in both men and women, and if present incidence rates continue, about 1 woman in every 14 may be expected to have breast cancer at one time or another during her life.

The assessment of therapy for breast cancer at the Ninth International Cancer Congress in Tokyo in 1966, and the Tenth International Cancer Congress in Houston, in 1970, gave equally disappointing results, and pointed out that there are many factors besides treatment which influence the results. The most significant observation indicated that there is no superior form of treatment for patients in all stages of the disease. The older thinking, that the Halsted-Meyer operation for carcinoma of the breast was the only adequate treatment, is no longer true. Many investigators believe that surgical therapy is being discredited because of poor results from radical mastectomy done indiscriminately, without regard to the clinical stage of the disease and with inadequate techniques. Optimum therapy requires the well-informed judgment of the surgeon, the radiotherapist, and the chemotherapist. At the Houston Congress less emphasis was placed on extended radical procedures, with new evidence supporting combined treatment.

In some centers, the classic operation has been supplanted by local or "modified" radical mastectomy, with and without irradiation therapy, while in other clinics, a more radical procedure known as "super-radical mastectomy" is being performed. Postoperative irradiation has been adopted as a routine adjuvant to surgical therapy by some surgeons, while others express doubt as to its efficacy. Recently, preoperative irradiation has proved to be of real importance, when combined with radical mastectomy for patients with regional extension of breast cancer.[96,97]

While hormone therapy and endocrine ablation have increased in importance with dramatic tumor regression at times, there is still uncertainty as to the precise indications for prophylactic or therapeutic hormonal treatment, and whether, for those undergoing such treatment, the advantage of benefits to the few outweighs the disadvantages to the many.

There has been a reduction in the mortality rate from breast cancer because of early diagnosis in an increasing number of patients. But there is a definite increase in incidence of breast cancer in premenopausal women, which counterbalances the better results with reference to the age-specific death rates.

Following treatment for carcinoma of the breast, 5-year survival without evidence of disease is not equivalent to cure, although statistics based on 5-year survivals form a

*Second Danely Slaughter Memorial Lecture, St. Francis Hospital, Evanston, Illinois, November 10, 1971.

useful index for comparing different groups of patients. The data, unhappily, indicate that mortality may continue to be "above normal" for a considerable period beyond the 5-year point.[25,26,71]

It is important, therefore, to reflect on the challenge which confronts us; to refresh our view of the problem by keeping in mind the natural history of the disease; to review such etiological factors as are known, at present; to understand the effects of tumor-host relationship; and to continually evaluate all of the available diagnostic and therapeutic measures, including those which are not used in routine practice and, especially, those with application of new concepts.

ETIOLOGIC FACTORS

The exact cause of cancer of the breast is unknown, but there are a number of factors which appear to be of significance, or appear to occur in excess in the history of women who develop the disease.

Endocrine Function

Bulbrook,[12] studying a high-risk population by biochemical means, pointed out a relationship between the clinical course of breast cancer and the amount *of 17-hydroxycorticosteroids* and *etiocholanolone* in the urine, expressed as discriminants. About half of a series of early breast cancer patients had negative discriminants 10 days after mastectomy. These patients had a recurrence rate of 75 percent in 8 years, compared with 33 percent for those with positive discriminants.[82,83]

Of particular interest is a preliminary report indicating that abnormalities in steroid excretion may be found in women in whom the disease is not yet clinically apparent. Although there is still much to be accomplished, the fact that such a close association exists between excretion of some steroid metabolites and some clinical aspects of the disease leads to cautious optimism that we may be able to develop the results of these findings into a diagnostic tool.

Pituitary Gonadotropic Hormones. As far as we know, pituitary gonadotropic hormones affect the human mammary gland indirectly through the gonads, by the production of two gonadotropins: the luteinizing hormone and the follicle-stimulating hormone. The luetinizing hormone is the key to ovulation and progesterone secretion by the corpus luteum, as well as to androgen secretion by the ovarian stroma. The follicle-stimulating hormone is responsible for the follicle development and, possibly, for its secretion of estrogen.[82]

Adrenocorticotrophic Hormones. Adrenocorticotrophic hormones are important since they foster the secretion of corticosteroids necessary for lactation. They probably are also responsible for secretion of estrogen and androgen from the adrenal cortex, thus supporting the continued growth of mammary neoplasms when present.[82]

Through the induction of mammary cancer in laboratory rodents, there is strong evidence of a primary role for pituitary secretion in certain types of cancers, which is corroborated by slowing of growth of experimental mammary tumors when hypophysectomy is performed.

Hypophysectomy. As expected, hypophysectomy in the woman with breast cancer also brings about some of the most dramatic and prolonged regressions in the disease. The reason for this favorable response remains speculative since some of these regressions are noted even with incomplete hypophysectomy. While it is known that the pituitary is necessary for the development of mammary carcinoma in laboratory rodents, the specific hormone responsible has eluded us until recently, when Pearson[72a,72b,99,100] and his co-workers reported that the essential hormone needed to stimulate breast cancer in rats is *prolactin*, and not estrogen. His group determined that a widely used tranquilizer, perphenazine, acts as an indirect stimulant of breast can-

cer in rats by raising the serum prolactin levels. After such tumors develop, and following hypophysectomy, the administration of estrogen fails to stimulate further tumor development. However, when bovine prolactin is administered, the tumor growth reactivates within 16 days. When prolactin injections are stopped, tumors again regress. Pearson et al.[72a,73b,99,100] believe that estrogen works as a cancer stimulant only indirectly, by regulating the pituitary gland's secretion of prolactin. A surge of prolactin secretion in the female rat was found just prior to ovulation. This surge was eliminated after ovariectomy and adrenalectomy. This and other related observations are felt consistent with the concept that ovariectomy-adrenalectomy induced regression of rat mammary cancer is related to reduction in serum prolactin levels, and that estradiol-induced reactivation of mammary tumor growth is related to rising serum prolactin levels.

The similarities between mammary cancer induced in the rat and hormone-responsive breast cancer in women suggests that the same endocrine factors may be operative in the human being. Although prolactin has not been isolated from the pituitary glands as a distinct hormone, Pearson, et al. feel there is considerable evidence that prolactin is a separate hormone in man.

Estrogens. There can be scarcely any doubt, however, that *estrogens* are concerned in the development and progression of certain human breast cancers.[4,11,19,28,34,72] Observation of patients with advanced breast cancer has shown that a considerable number of the tumors are estrogen-stimulated. Alteration of endocrine environment by means of castration and other endocrine ablative procedures, or by giving antagonistic sex steroids, is therapeutically beneficial in endocrine target-sensitive human breast cancers (approximately 45 percent). The overtones of endocrine influence are also observed when one considers the natural history of the disease.

The death rate from mammary cancer, as revealed in general mortality statistics, is higher for single women than for married women of the same age. Married women, after the child-bearing period, show a higher mortality rate among childless women than among those who have had children.[6,13,14,15] It is expected that the number of women dying of breast cancer will increase, because longevity in general has been prolonged. With the exception of the ages between 50 and 60 years, there is an increasing *incidence* of cancer in the later decades. This feature is more marked in single than in married women.[86,87] It seems, however, that the chances of *dying* of breast cancer at any age past 50 have been steadily declining with each successive generation. Slightly more than 55 percent of women with breast cancer have not reached menopause. There is no certain explanation for this epidemiologic finding. It may reflect the influence of active endocrine functions in the child-bearing period and the changes in these functions at menopause. Remarkable regression in breast cancer is known to take place at the natural menopause, and a few patients treated by hormone therapy during this period have had the disease controlled for the longest duration. Most cases of spontaneous regression of breast cancer have also been reported in women of menopausal age.

Mammary Dysplasia, Certain Benign Tumors. The abnormalities in *mammary dysplasia* (the result of abnormal endocrine stimulus) and the presence of certain *benign tumors* (e.g., fibroadenoma and intracystic papilloma) have been regarded by numerous investigators as some of the bases for the development of mammary carcinoma.*

In our experience with 300 patients who had adenosis, associated breast cancer was found in 12 patients (4 percent). A 6 percent incidence of breast cancer was found asso-

*References 2, 7, 17, 38, 39, 58, 60, 63, 84, 90, 94.

ciated with intracystic papilloma.[18,19,20] Dublin[31] has calculated the risk of mammary cancer in the normal population of the same age groups, for a period of 10 years, to be 0.42 percent.

Aging Process

The age-distribution curve, showing the relative frequency of women with mammary cancer, does not reflect the true relative age risk of developing mammary cancer in the total population. The true relative age-risk figures must come from data using not only the number of cases of cancer encountered at a specific age, but also using those of the total related population in the same age "exposed to risk." An incidence curve based on this concept shows that the development of cancer of the breast increases from early age and goes steadily up to the end of the span of life. The probability of mammary cancer in women between the ages of 75 and 79 years is more than 10 times as great as between the ages of 35 and 39 years.)[25,26] This points up the strong probability that cancer is to some degree an abnormal product of the degenerative process, associated with aging of the tissues. This does not preclude a variety of other intrinsic and extrinsic factors.

Genetic Considerations*

Dr. David Anderson† of M. D. Anderson Hospital points out that investigations with inbred strains of mice have established the etiologic importance of genetic factors in mammary tumor development. The actions of some genes are localized in the physiology of hormone production by the ovary; other genes control the response of the mammary tissue to hormones; and still others, probably few in number, are important in the propagation and transmission of the mammary tumor agent (or virus).[8,9] In man, to date, the possibility of having such genes is generally questioned or discounted which is surprising since genetically determined cancers occur frequently and have important practical relevance to early detection.

Three basic methods can be utilized for detecting a genetic variety of cancer: (1) a retrospective statistical approach comparing the frequency of a given type of cancer in relatives of cancer patients to its frequency among relatives of control patients, (2) a pedigree approach whereby available relatives are examined and occurrences of a given type of cancer are verified through medical documentation, and (3) a comparison of the concordance and discordance of a given type of cancer in pairs of monozygotic and dizygotic twins.

A pedigree approach by Anderson[1] has been designed to provide answers to some of the unresolved genetic questions related to human breast cancer. This study is being directed to families with two or more affected relatives. Of the 5,755 breast cancer patients seen at M. D. Anderson Hospital, it was ascertained that 399 patients had one or more affected relatives with breast cancer. Anderson has found that a number of familial patients are significantly younger at first admission and have a higher frequency of bilateral lesions than nonfamilial patients. The histopathology of the breast lesions reveals a significant number diagnosed as medullary carcinoma, intraductal carcinoma, and lobular carcinoma.

Within the familial group, preliminary evidence indicates the possibility of two subgroups: One is characterized by an early age distribution, and the other by a later one. The latter group is confined to patients with obesity, hypertension, and diabetes. Endocrine studies will be made to determine whether the early age type is associated with the insufficiency of ovarian estrogen or androgen, or both, and the later age type with adrenocortical imbalance. These studies may ultimately help to indicate whether breast cancer is comprised of one or more subtypes which might be distin-

*References 13, 53, 62, 70, 73, 86, 90.

guishable by clinical, pathologic, endocrine, or genetic characteristics, or all four.

Location of the Primary Breast Cancer

Location of the primary breast cancer as a factor in survival is a real one, when the sites are divided between the medial and outer hemispheres of the breast.[6,39,46-48,68,79,97] A comparatively bad prognosis obtains for inner-half lesions, as opposed to outer-half tumors, in the early stages of the disease. Once cancer has progressed to an extent that the axillary lymph nodes are involved, the better prognosis of lateral hemisphere lesions is no longer valid and there is approximately the same number of 5-year survivors. Medial hemisphere lesions, per se, lead to more frequent involvement of the parasternal lymph nodes than do lateral lesions. Clinically, many cases with positive substernal lymph nodes are mistakenly placed in the favorable stage I classification which, by the same token, reduces the 5-year survival rate in stage I.

Size of the Tumor and Histopathology

The size of the tumor, as an expression of the duration of symptoms and the rate of growth,[50] often determines the extent of disease and the character of the findings on examination.[39] The infiltrative pathologic types of mammary cancer, i.e., scirrhous carcinoma, spheroidal cell cancer, carcinoma simplex, tumors arising from small ducts or acinar structures, and rapidly invading stroma, show a fairly definite correlation between the size of growth and duration of symptoms. The smaller the size, the better in general is the prognosis, except where biologic predeterminism[64] or biologic variation in growth potential plays a role. In patients with infiltrative forms of cancer who survive 5 years or more (55 percent), the average size of the tumor is 2.5 cm. If one plots the 5-year survival rates of this group against the size of the tumor and the duration of symptoms, the survival rates are inversely proportional to both the size of the tumor and duration of symptoms.

In the circumscribed forms of mammary cancer (papillary adenocarcinoma, gelatinous carcinoma, and comedo carcinoma), slow growth is the rule. These tumors are often 5 cm or more in diameter and of more than a year's duration when first seen. The tumor remains for a long time circumscribed, bulging, and movable over deep structures. For example, the average size of 154 papillary breast cancers at the end of 16 months was 5.8 cm, with a postoperative 5-year survival rate of 55 percent. Similar lesions 2.5 cm in diameter had a duration of 3 months, with a postoperative 5-year survival rate of 78 percent.

Regional Lymph Node Involvement

Regional lymph node involvement is obviously an important factor in prognosis of breast cancer. The main route of spread for lymphatic metastases is through the axilla. Indeed, other anatomical locations of lymphatic spread have tended to be overlooked. Dahl-Iversen[27] and his associates (1951 and 1952) reported 5.3 percent positive supraclavicular nodes among 76 patients who had supraclavicular lymph node dissection at radical mastectomy. The series was made up of comparatively favorable cases with axillary metastases in 43 percent of the patients, and with internal mammary nodes involved in only 29 percent. Failure to recognize the significance of associated axillary and supraclavicular lymph node metastases is due to the teaching that the axillary and supraclavicular nodes are two independent groups.[48]

The other principal direction of lymphatic spread is to the internal mammary lymph nodes. Handley et al. have demonstrated the importance of this route of spread.[46-48,96,97] When the axillary lymph nodes are involved, the internal mammary lymph nodes often have metastatic cancer. The greater the degree of axillary involvement, the more likely is the internal mam-