A REPORT TO THE PHYSICIANS OF TEXAS

newsletter

THE UNIVERSITY OF TEXAS SYSTEM CANCER CENTER

March-April 1980 M. D. Anderson Hospital and Tumor Institute Volume 25, Number 2

Predisposition to Breast Cancer Reviewed

David E. Anderson, PhD*

Whether the clustering of breast cancer in families represents inheritance of susceptibility or the exposure of family members to some common cultural, dietary, or other environmental stimulus is still being debated. There is abundant and convincing evidence of a genetic basis for the disease, and equally compelling is the evidence for an environmental basis. This dichotomy of evidence is probably created by thinking of breast cancer as a single disease with a single cause. There are, however, at least two categories—premenopausal, primarily influenced by genetic determinants, and postmenopausal, influenced most by extrinsic factors.

This concept is supported by the fact that wide international differences in incidence and the northern predominance of the disease in the United States, both of which are measures of extrinsic environmental factors, apply primarily to postmenopausal women. Results from other studies have shown that a late age at first parity, nulliparity, low parity, and obesity mainly relate to postmenopausal breast cancer, while an early age at menarche, a high socioeconomic status, and a family history of breast cancer are characteristics of premenopausal disease.

The association of high familial risks with premenopausal and/or bilateral disease is evidenced by the following:

- Patients with a familial risk have a significantly earlier average age at diagnosis than unselected patients.
- Patients with a familial risk have a significantly higher frequency of primary cancer in both breasts than unselected patients, and this frequency is most pronounced for those diagnosed premenopausally.
- Premenopausal diagnosis and bilaterality in a patient increase the risk to her female relatives 8.8-fold, whereas postmenopausal or unilateral disease or both are associated with risks of only 1.2-fold to 1.5-fold.
- Lifetime probabilities of 11% to 32% for developing breast cancer are obtained when pedigrees are classified into three groups according to family history: patient's mother, sister, or second-degree relative had breast cancer. The probabilities are highest (27% to 32%) for sisters and daughters of patients with affected mothers. The disease in this high-risk group is characterized by early onset, whereas sisters and daughters of patients with affected sisters or second-degree relatives with lower probabilities of 11% to 14% are characterized by late onset.
- A further classification of these pedigree groups according to age at diagnosis and bilaterality in the patients indicated that the lifetime probability of breast cancer in the sisters of patients with premenopausal and bilateral disease is near 50%; probabilities for sisters of patients with postmenopausal and unilateral disease range from 5% to 10% (6% to 7% probabilities are reported for women in the general population).
- Early age at onset or diagnosis and tumor multiplicity are two characteristics of other inherited forms of cancer.
- The families characterized by a 50% lifetime probability of developing breast cancer may develop one of three different inherited types. The first is characterized by very early onset, usually between 25 and 35 years of age, a high rate of bilaterality, and the occurrence of associated familial tumors—brain tumors, soft tissue sarcoma, leukemia, thyroid tumor, or other tumor types. The second inherited type has the same characteristics as the first, except the occurrence of associated tumors is limited to ovarian cancer. The third type is similar to the others, but age at diagnosis, though premenopausal, is later and no associated malignant neoplasms are involved.

Environmentalists may contend that the 27% to 32% lifetime probabilities, or the 50% probability when a distinction is made for age at diagnosis and bilaterality, are high because the relatives at risk were exposed to a similar environment. Granted that relatives may have had the same exposures, but studies have shown that the only relatives at risk of the three pedigree groups were the patient's sisters, thus outweighing environmental influence theories. Any exposures should have been

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Bertner Award Goes to MDAH Scientist

T. C. Hsu, PhD, MDAH professor of biology and chief of the section of cell biology, received the Ernst W. Bertner Memorial Award March 4 at the 33rd Annual Symposium on Fundamental Cancer Research at the Shamrock Hilton Hotel in Houston. The award went to Dr Hsu for his overall contribution to cell biology and cancer research.

Established in 1950 to foster the development of outstanding cancer research, the award was named for MDAH's acting director from 1942 to 1946. This was the first time that the Bertner Award went to a MDAH staff member.

Dr Hsu is credited with making modern chromosome study possible with his 1952 "discovery" of the hypotonic method of spreading mitotic mammalian chromosomes so that they could be accurately counted and characterized for the first time. Dr Hsu's discovery resulted from a laboratory error in which a hypotonic—not isotonic—solution was used to wash cell cultures. The error made the spreading possible.

Dr Hsu's contributions span from his discovery with MDAH's Frances E. Arrighi, PhD, of the C-banding technique of staining, to his studies with B. R. Brinkley, PhD, with electron microscopy that elucidated nuclear component ultrastructure, to his discovery in mammalian phylogeny of closely related species' chromosome variability, to his development of a cellular materials catalog useful to biomedical researchers.

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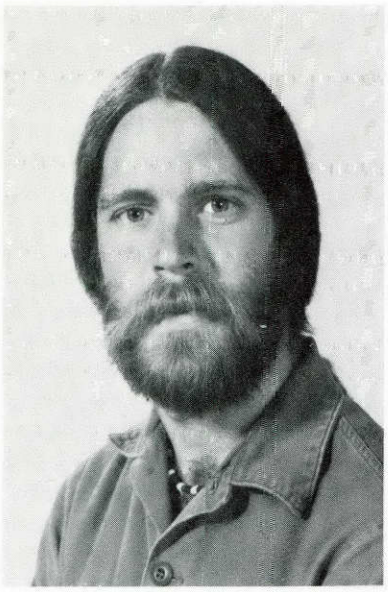

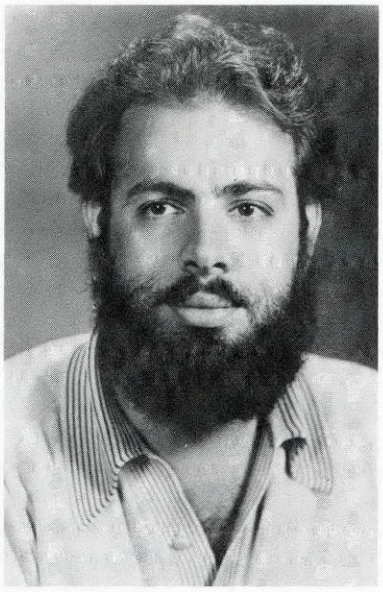

Wilson S. Stone Memorial Award winners Marc S. Collett, PhD (far left), of the University of Colorado at Denver, and former University of Texas graduate student Peter T. Lomedico, PhD (near left), now of Harvard, accepted the award at the 33rd Annual Symposium on Fundamental Cancer Research. The presentation was the first time the annual award honored two recipients.

Two Students Accept Stone Award Honors

In an unprecedented move, the Wilson S. Stone Memorial Award was presented to not one but two student scientists March 4 at the 33rd Annual Symposium on Fundamental Cancer Research. The award, presented annually, recognizes superior achievement in the biomedical sciences by students in the United States.

The winners are former University of Texas graduate student Peter T. Lomedico, PhD, now at Harvard, and Marc S. Collett, PhD, a postdoctoral fellow at the University of Colorado Health Sciences Center at Denver who earned his BS and PhD degrees from the University of Michigan, Ann Arbor. Each received his PhD degree in 1977.

Dr Lomedico, in predoctoral work at The University of Texas Health Science Center at Houston Graduate School of Biomedical Sciences, isolated undegraded messenger RNA and began in vitro protein synthesis experiments. According to MDAH biochemist Grady F Saunders, PhD, who supervised the winner's predoctoral research, Dr Lomedico was the first to show a 23 amino acid sequence (now called the signal sequence) on the NH_2-terminal end of the proinsulin translation product. Signal sequences are found on a variety of secreted proteins and are thought to be involved in the process of secretion through the cell membrane.

At Harvard, continuing to pursue his interest in insulin, Dr Lomedico isolated the chromosomal rat preproinsulin gene. Through DNA sequence analysis of this gene, he completed the primary structure determination of the preproinsulin mRNA, established a complete amino acid sequence for the preregion of preproinsulin, predicted that the primary gene transcript must be processed to yield the mature mRNA, and developed a testable model to show how introns evolve.

The award honors co-recipient Dr Collett for work on the structure and function of the Rous sarcoma virus transforming gene product, $pp60^{src}$. He has made significant contributions in the identification, purification, and characterization of $pp60^{src}$, as well as its mode of action.

Pathology professor Raymond L. Erikson, PhD, of the University of Colorado Health Sciences Center, said in describing Dr Collett's work that not only do his studies begin to allow description, in biochemical terms, of the pathways that lead to malignant transformation for at least one experimental system, but his results may be important for learning the course of normal cell functions.

Dr Lomedico is a former University of Texas System Cancer Center Rosalie B. Hite Predoctoral Fellow and a former fellow of the Juvenile Diabetes Foundation. Dr Collett, a former Damon Runyon-Walter Winchell Cancer Research Fellow, is now a special fellow of the Leukemia Society of America.

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Noteworthy

A registered nurse who has a degree in mechanical engineering has been appointed MDAH's first biosafety officer. **Lola Bilowich,** BS, MS, a veteran of Dr Denton Cooley's heart team and a former MDAH infection control nurse, becomes responsible for planning disposal and storage of toxic substances used in research projects in order to meet government standards for handling biologically hazardous materials.

Cancer, Genetics Symposium Meets

The 33rd Annual Symposium on Fundamental Cancer Research, "Genes, Chromosomes, and Neoplasia," was held March 4–7 at the Shamrock Hilton Hotel in Houston. Over 25 scientists presented papers that described techniques for exploring the relation between genes and chromosomes and cancer and that summarized the resulting current knowledge about this relation.

Held annually to bring together scientists working on one aspect of cancer research for information exchange and discussion, the symposium attracts physicians and scientists from across the United States and foreign countries. This year over 700 attended.

The four-day symposium was divided into six sessions and featured the presentation of the Ernst W. Bertner Memorial Award and the Wilson S. Stone Memorial Award at the opening assembly. MDAH's T. C. Hsu, PhD, received the Bertner Award. Recipients of the Stone Award were Marc S. Collett, PhD, of the University of Colorado Health Sciences Center, and Peter T. Lomedico, PhD, of Harvard University. The awards are presented annually.

The first two sessions, "Chromatin and Chromosome Structure" and "The Sarc Gene," included examination of techniques for studying cell behavior, the molecular structure of genes, and the oncogenicity of retroviruses.

In session III, "Gene Expression," MDAH researchers reported on investigations of the cytoplasmic physiologies that accompany or direct the early events in malignant transformation. Other researchers discussed the nature of gene variation and gene transfer in somatic cells, gene phenotype switches caused by genotypic events, and the search for useful markers for malignancy. Discussion of gene organization in cells and sensitivity to antineoplastic drugs was part of session IV, "Gene Amplification."

There were seven presentations during the session "Chromosomal Changes Associated with Neoplasia." Scientists discussed consistent chromosome abnormalities in patients with primary and metastatic tumors, lymphoma, and leukemia. They described changes in malignant cells, chromosomes, and cellular DNA content and the relationship between these changes and treatment, genetic predisposition, and other variables.

The final session, "Genetics of Cancer," included studies of the relationship between somatic mutation and genesis of neoplasia, and a population-based assessment of familial cancer risk in Utah Mormon genealogies. The head of the National Cancer Institute's Clinical Genetics Section concluded the presentations with a report on genetic, familial, and congenital conditions that predispose people to cancer and what identification of those conditions means to prevention and control.

Chairpersons for the symposium were Frances E. Arrighi, PhD, and T. Elton Stubblefield, PhD, both of the Department of Biology, and Potu N. Rao, PhD, from the Department of Developmental Therapeutics.

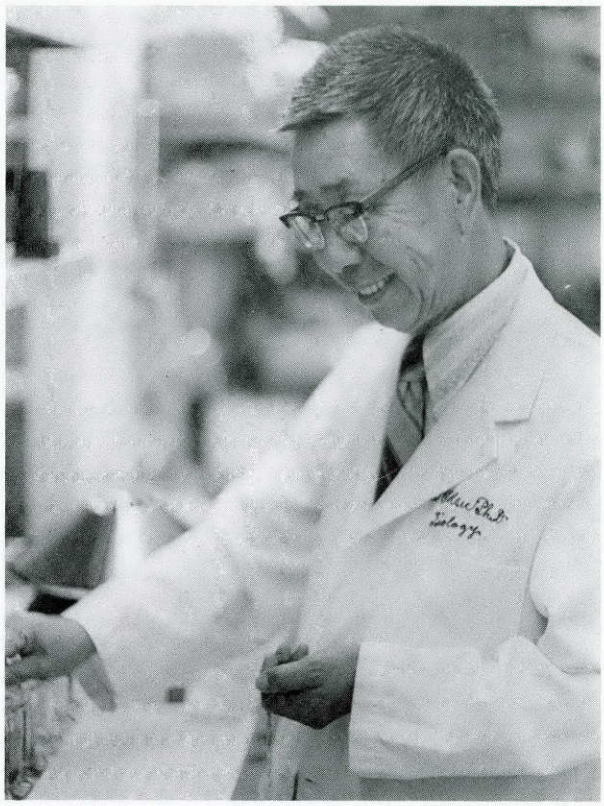
MDAH sponsored the meeting. The National Cancer Institute and the American Cancer Society, Texas Division, Inc., cosponsored the symposium in cooperation with The University of Texas Health Science Center at Houston Graduate School of Biomedical Sciences.

Raven Press will publish the proceedings.

Bertner Award . . .

Continued from page 1

A native of China, Dr Hsu went to The University of Texas at Austin in 1948 and completed his PhD degree in a record two years and nine months. After working at The University of Texas Medical Branch in Galveston, Hsu came to MDAH in 1955 as an associate biologist. Dr Hsu holds the Olga Keith Wiess Chair for Cancer Research, named in honor of the longtime MDAH benefactress. Author of more than 200 scientific articles, Dr Hsu has edited multiple volumes of chromosome atlases, served on editorial boards of journals such as *Cytogenetics* and *Cancer Research,* and most recently authored the book *Human Mammalian Cytogenetics: An Historical Perspective.*



Bertner Award recipient T. C. Hsu, PhD, holding a stopwatch in his left hand, checks an experiment in the cell biology laboratory. Dr Hsu is the first MDAH scientist to receive the award.

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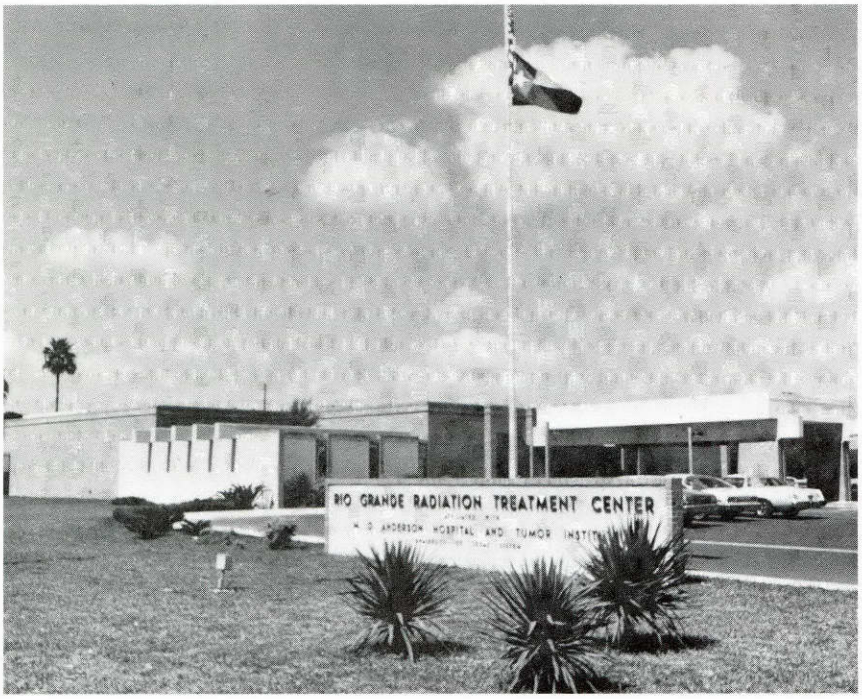


The Rio Grande Cancer Treatment Center (left), a 13,500-square-foot facility set on three acres in McAllen, recently acquired 10 additional acres adjacent to the Center site and a two-story house, which currently accommodates the women's auxiliary. The Center only recently changed its name, replacing *Radiation* with *Cancer*, to reflect the broader services it now offers.

Valley Center Begins Fourth Year

The Rio Grande Cancer Treatment Center, located in McAllen and operated and staffed by MDAH, begins its fourth year of operation this spring. Offering radiotherapy and chemotherapy to cancer patients in a 10-county South Texas area, the Center boasts increases in personnel, facilities, and land since its opening, and plans propose a pharmacy, an X-ray unit, and expansion of the clinical laboratory.

The Center was created through an agreement between the nonprofit Rio Grande Radiation and Cancer Research Foundation, The University of Texas System Board of Regents, and MDAH. MDAH supplies and trains the staff, and the Foundation provides the facilities. The Center registered its first patient in May 1977, according to business administrator Steve Villegas, and was in complete operation by June. About 350 miles from MDAH, the Center meets the needs of Rio Grande Valley cancer patients by providing high-caliber treatment close to home.

More than patients profit by the Center's location, according to Joseph T. Painter, MD, MDAH vice president for resource planning and evaluation. "The Center is a community resource for doctors and patients alike," he says, "making it possible for many patients to maintain a normal lifestyle while receiving outpatient treatment for their disease." In addition, the Center's services extend to "Winter Texans," retirees from cold climates vacationing in South Texas, who practically double the Center's patient population during winter and spring.

Ahsen Ozarda, MD, clinical director of the Center, says the number of staff physicians has increased to three since the center opened with only one in 1977. Growth in the number of clerical and clinical personnel has paralleled the increase in services. The addition of a chemotherapy module forced the Center to change its name from Rio Grande *Radiation* Treatment Center, the name under which it opened, to Rio Grande *Cancer* Treatment Center. "With the addition of a chemotherapist to our staff, we are able to offer complete outpatient treatment," says Dr Ozarda, who hopes to add a drug dispensary within the next three months to provide specialized drugs to patients undergoing chemotherapy.

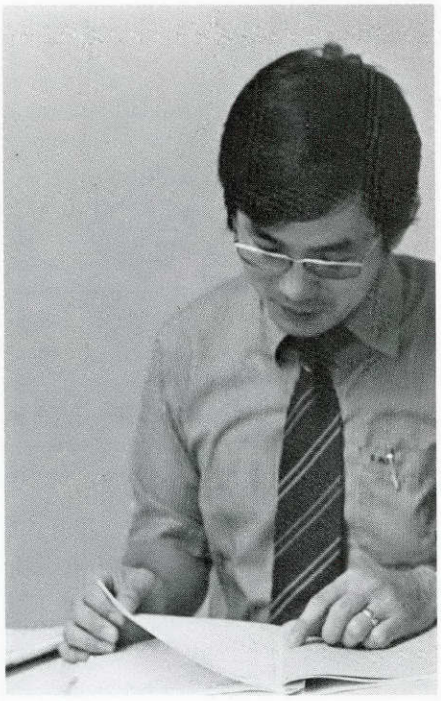
Radiotherapy equipment for the Center includes a Clinac 18

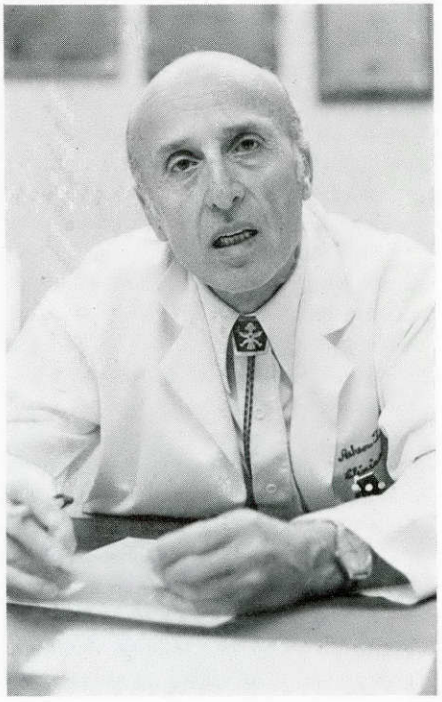
Lectures Presented in Oncology Series

The University of Texas System Cancer Center is offering a 30-lecture series instructing participants in ways basic science knowledge is applied to clinical research in cancer. Held at the MDAH auditorium on Fridays and Saturdays, the lectures are open to all interested physicians at no cost.

Called "Fundamentals of Oncology—Part II: Application of Basic Science to Clinical Research," the program is the second part of the "Fundamentals of Oncology" program initiated last year. The lectures are presented by staff members of MDAH, the Graduate School of Biomedical Sciences, and the Health Science Center Medical School (HSCMS). Each lecture meets the criteria for one credit hour of the Physician's Recognition Award of the American Medical Association, and participants need not register in advance.

Lectures yet to be presented are listed below. Topics include principles of surgical physiology in cancer therapy, supportive care of the cancer patient, and immunologic and biologic therapy. Friday lectures are held from noon to 1:30 p.m., Saturday lectures from 8:30 to 10 a.m. All speakers are from MDAH unless noted otherwise.





At work at the Rio Grande Radiation Treatment Center, associate radiotherapist Dong W. Oh, PhD (near right), reads a patient's chart. Far right, Ahsen T. Ozarda, MD, the Center's clinical director, explains the facility's functions. Beginning its fourth year of operation this spring, the McAllen Center now offers complete outpatient treatment to residents in a 10-county South Texas area.

linear accelerator (a 10 million-electronvolt unit with electron beam capabilities), an AECL cobalt machine, and a 250-kilovolt orthovoltage unit for treatment of skin lesions. In cooperation with nearby hospitals, radium implant therapy is available, according to Dr Ozarda.

Recent acquisitions of the 13,500-square-foot Center include 10 acres of land adjacent to the Center's three-acre site and the two-story Baker House, currently used as headquarters for the more than 60-member women's auxiliary. It is eventually intended, according to Dr Ozarda, for housing visiting speakers, residents, or fellows. The land may accommodate Center expansion.

Dr Ozarda says other plans include continued expansion of the "small but effective" clinical laboratory and addition within 1980 of a diagnostic X-ray unit. He says that presently patients must return to their cities of residence in order to have diagnostic X-ray films made, a process delaying diagnosis sometimes a week or more.

The Center was designed to serve 10 counties, enclosed in a triangle formed by Corpus Christi, Laredo, and Brownsville, including Kennedy, Willacy, Cameron, Duvall, Brooks, Hidalgo, Webb, Hogg, Starr, and Zapata counties.

May	Subject and Lecturer
3	Dentistry for the oncology patient; Bela B. Toth, DDS, MSc, and Gordon E. King, DDS, Dental Oncology
9	The supportive care of the cancer patient; Kenneth B. McCredie, MB, ChB, Developmental Therapeutics
10	Prevention and therapy of infectious complications of cancer and their treatment; Gerald P. Bodey, MD, Developmental Therapeutics
16	Basic clinical principles of hyperalimentation
17	Clinical cancer immunology I: Immunodeficiency and immunosuppression; Evan M. Hersh, MD, Developmental Therapeutics
23	Clinical cancer immunology II: Tumor antigens and tumor immunity; Barry D. Kahan, MD, PhD (HSCMS), Surgery—Organ Transplantation
24	(a) Cell surface markers and receptors in clinical cancer immunology; Samuel G. Murphy, PhD, MD, Developmental Therapeutics; (b) Principles of immunodiagnosis of cancer; Giora M. Mavligit, MD, Developmental Therapeutics
30	Principles of immunotherapy and biological therapy of cancer; Stephen P. Richman, MD, Developmental Therapeutics
31	Interferon as a biological response modifier in man; Jordan U. Gutterman, MD, Developmental Therapeutics

Urology Department Sets Fifth Annual Seminar

The MDAH Department of Urology has set its Fifth Annual Urologic Oncology Seminar for August 21–23 at Houston's Shamrock Hilton Hotel, according to Douglas E. Johnson, MD, head of MDAH's Department of Urology.

Eleven speakers, all from MDAH, will review the various urologic malignant diseases and emphasize multimodal therapy as it is practiced at MDAH. The meeting's faculty is drawn from departments throughout the institution, including Urology, Pathology, Radiotherapy, Medicine, and Pediatrics.

Last year 255 registrants from 29 states and five foreign countries attended the annual meeting.

Open to physicians outside MDAH, the meeting meets the criteria for 18 credit hours in Category I of the Physicians Recognition Award of the American Medical Association.

For registration information write to the Office of Education, Room W-718, M. D. Anderson Hospital, 6723 Bertner, Houston, Texas 77030.

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Breast Cancer Growth Uniform, Then Random

H. Stephen Gallager, MD*

The natural history of early stage breast cancer can be viewed as a group of events that take place serially. This concept is inferential since no method exists that can reproduce the process in vitro or follow it in vivo without interfering with its progression. Breast cancer is a disease of mammary epithelium. The entire mammary system is embryologically derived from ectodermal downgrowths into the mammary fat pad. The ducts and their terminal expansions are a complexly invaginated but continuous epithelial surface.

Mammary epithelium grows rapidly around the time of menarche; fluctuates with the menstrual cycle throughout reproductive life; undergoes physiologic hyperplasia and regression during pregnancy, lactation, and puerperium; and gradually atrophies after menopause. Because it has such an active cell population, opportunities for genetic mutations that produce cells capable of neoplastic proliferation abound. This leads one to believe the initial event in the development of breast cancer occurs premenopausally, even though clinical manifestation may be long delayed. Studies of human mammary carcinoma growth rates and epidemiologic data showing an increase in incidence in women under 50, both paralleling improvement of detection techniques, support this concept.

A subserial whole-organ sectioning study of 200 specimens showed that breast carcinoma is regularly accompanied by ductal and lobular epithelial changes that are not histologically neoplastic. Lesions ranging from simple hyperplasia to hyperplasia with cytologic atypia to frank noninvasive carcinoma were usually found in each specimen.

From these findings it was hypothesized that epithelial hyperplasia is a nonobligatory form of preneoplasia: that neoplastic transformation regularly follows ductal or lobular epithelial hyperplasia or both. However, hyperplasia, a frequent finding in benign breast biopsies, is not followed inevitably by carcinoma development. Therefore, it has been thought to have other possible outcomes, such as the various lesions of the fibrocystic disease complex, persistent hyperplasia, reversion to a normal state, and atrophy.

NATURAL HISTORY OF HUMAN BREAST CANCER

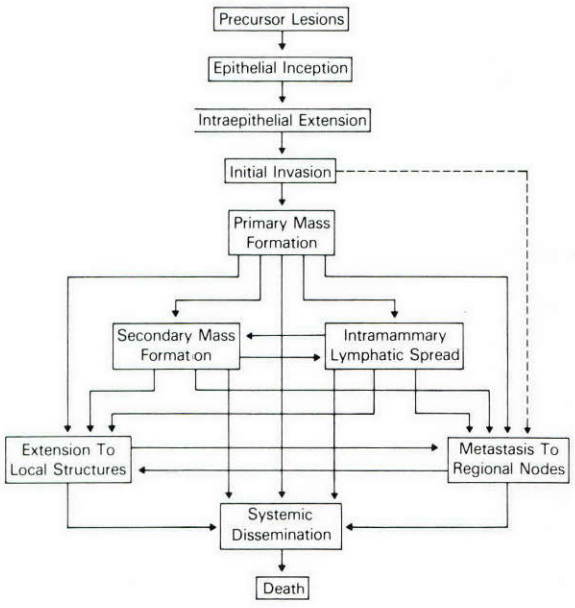

Figure 1: This flow chart outlines the sequence of events in the natural history of breast cancer.

A specific pattern of hyperplasia, appearing to result from the unfolding of a lobule and its accompanying terminal duct, is found in many breasts containing invasive carcinomas. These hyperplastic terminal groupings with atypia may be the same as M. M. Black's "precancerous mastopathy." Recently, others demonstrated a strong correlation between the presence of hyperplastic terminal groupings and the dense parenchyma mammographic pattern that may be a potent predictor of subsequent breast cancer. Therefore, evidence mounts that this form of hyperplasia is closely related to mammary carcinogenesis and may be specifically preneoplastic.

Noninvasive intraductal carcinoma and lobular carcinoma in situ are the earliest recognizable lesions of breast cancer, but they histologically resemble atypical hyperplasias, making diagnostic confusion commonplace. Unfortunately, no reliable marker exists that specifically distinguishes between cells committed to neoplastic growth and those that are not. A recent report claims that explants of breast cancer tissue produce neovascularization in rabbit corneas but that benign tissues do not. The small volume of most problematic lesions and the difficulty in identifying and isolating representative tissue without denaturing it would hinder clinically useful testing based on this information. Diagnosticians face a "gray zone" existing between atypical hyperplasia and the earliest conceivable carcinoma.

Once neoplastic transformation establishes itself, growth proceeds within the epithelium of origin before invasion occurs, a phenomenon common to all types of intraepithelial carcinoma but not readily observable in the breast's geometrically complex tissues. Intraductal carcinoma may spread both proximally and distally and may involve lobules, and in situ lobular carcinoma may extend to terminal ducts. Implicatons of a study showing that intraductal carcinoma involvement may be continuous or discontinuous within a single duct and its branches are that (1) progressive neoplastic transformation of duct lining cells results in intraductal extension and (2) subpopulations of cells incapable of responding to the carcinogenic stimulus exist, a finding supported by cell kinetics studies.

The point of initial invasion is another "gray zone." In patients with apparently noninvasive intraductal carcinoma, axillary nodal metastasis occurs with an incidence of 6% to 9%. These cases may be explained on the basis of limited sampling of breast tissue for histologic examination, but in some it is indisputable that no lesion recognized as invasive carcinoma exists. In one study, two patients each presented with a single enlarged axillary node containing metastatic carcinoma, but breast specimens showed only noninvasive intraductal carcinoma, although the examination technique would have revealed any invasive nodule larger than 0.5 mm.

The obvious conclusion is that some invasive carcinomas

maintain the configuration of noninvasive intraductal carcinoma, but conventional histologic examination is inadequate to identify them. Electron microscopic examination has demonstrated gaps in the basal laminae of mammary ducts and has shown that ameboid prolongations of neoplastic cells in intraductal carcinoma may extend through the apertures into adjacent tissues. If cells completely escape this way from their intraepithelial position, they are readily available for lymphatic transport to nodal depots since intramammary lymphatic vessels closely parallel ducts.

To this point, the evolution of breast carcinoma is fairly uniform, but significant volumes of invasive neoplasm create a great diversity (Fig. 1). Cell content and structure of masses vary widely. Rapidly dividing cells invade explosively from multiple adjacent sites and form multinodular masses by coalescence. Less active cells ooze through duct walls into fibrotic periductal tissue and produce the familiar stellate mass. Indolent cells expand and erode basement membranes, resulting in comedocarcinoma. Structures may be modified by metaplasia, accumulation of cell products, or reticuloendothelial cell proliferation related to host response. Secondary masses may form as a result of additional foci of invasion from intraepithelial disease or from intramammary lymphatic transport of cells to regions of the breast remote from the initial mass. As tumor burden increases, the probability of extramammary extension and metastasis rises progressively, and the possibility of achieving control decreases proportionately. This concept of breast cancer evolution has prompted the current emphasis on early detection and treatment. During preinvasion and probably through initial invasion, the disease course is highly predictable, and local treatment methods are highly effective. Repeatedly, adequate treatment of breasts with lesions believed to represent these early stages has resulted in five-year disease-free survival rates exceeding 90%.

Little is known about the time required for breast carcinoma to progress from epithelial inception to mass formation, but it is usually several years, although it may vary widely. Efforts at breast cancer control through early detection have critics who object on grounds that cancers discovered by screening techniques are not life-threatening. They see intraductal carcinoma and lobular carcinoma in situ as special kinds of carcinomas, not as stages in progression toward invasion. They argue that these kinds of cancers are readily controllable by immunologic mechanisms and persist unchanged for many years. They believe life-threatening, "interval" carcinomas grow from epithelial inception to primary mass formation rapidly enough to become potentially metastasis-producing within the interval between screenings.

Although it is too early for survival statistics to be meaningful, work by the Breast Cancer Detection Demonstration Project shows little difference in size, differentiation, or frequency of nodal involvement between "interval" cancers and those detected by screening. Therefore, since development is unpredictable once invasion occurs and local treatment methods are most effective in early stages, efforts directed at early detection are thoroughly justified.

*Department of Pathology, MDAH. (The complete text of this article is forthcoming in *Cancer*. Physicians requiring more information on this topic should contact the author—ED.)

Predisposition . . .

Continued from page 1

similar in the three groups, yet only one of the pedigree groups had high risks. Furthermore, high risks applied not only to the sisters of patients but to the daughters of these same patients, whereas the daughters of the patients in the other two pedigree groups again had low risks.

In addition, all pedigrees (patients) were selected from the same population of patients and for the same reason (family history of breast cancer), and all pedigrees and patients were documented during the same time interval by the same personnel. In spite of these similarities, only the high-risk group was characterized by an early average age at diagnosis, particularly patients with bilateral disease. Also, age at diagnosis (*not* time) was significantly correlated among affected sisters only in the high-risk group. These findings convincingly argue against an environmental explanation for the high risks or some sampling peculiarity. The high risks must reflect a genetic effect, an effect transmitted from an affected mother to her daughters, meaning approximately 30% of the daughters will subsequently develop the disease; however, if the disease in the mother and patient developed in the premenopausal period and bilaterally in one or the other, the probability then increases to 50%.

Factors responsible for increased risks in the inherited types of breast cancer have not been identified. No consistent and well-defined differences have emerged from comparisons of patients (or their relatives) with matched controls regarding lymphocyte 16 alpha-hydroxylase activity; plasma estradiol, progesterone, or prolactin; urine estriol ratio; or the estriol proportion. Last year, however, researchers reported significantly lower levels of urinary estrogen glucuronides in premenopausal women from high-risk (breast and ovarian cancer) families compared to control women matched for age, height, and reproductive history.

In 1977 N. L. Petrakis proposed a general genetic-environmental model for breast cancer to explain the risks in Caucasian women compared to those of Oriental women. Cerumen (ear wax) type is an inherited trait in which the allele for the wet type (secretory) is dominant to the dry. The alleles that determine cerumen type are also thought to affect breast secretory activity. In Petrakis' hypothesis, the turnover rate of secreted sub-

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A recently passed bill of the Texas State Legislature requires that all recipients of publications from state agencies reaffirm, in writing, their interest in continuing to receive the publications. Since the *Newsletter* falls within the definitions of the bill, you must return the enclosed postage-paid postcard to continue receiving the *Newsletter*.

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Predisposition . . .

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stances and their rates of resorption are the primary determinants of the degree of exposure of the breast epithelium to endogenous and environmental mutagens and carcinogens. Oriental women, at low risk to breast cancer, characteristically have a high frequency of the dry allele, decreased breast secretory activity, and therefore minimal exposure to these agents. Caucasian women, at high risk to breast cancer, have a high frequency of the wet allele, increased breast secretory activity, and therefore prolonged exposure.

Although the nature of gene action in the hereditary forms of breast cancer is not known, the forms have important relevance to early detection, treatment, and prevention. That breast cancer can be detected at a higher-than-expected rate in women at high risk for the disease because of a family history of breast cancer is demonstrated by the results of a screening program. Female relatives of breast cancer patients underwent a physical breast examination, thermography, and mammography. Breast cancer was detected in 2.8% of women of all ages and 4.2% of those age 35 and older. In contrast, screening of women who had family histories of large bowel cancer disclosed breast cancer in only 0.88% of women of all ages and 1.2% of those 35 years and older. Clearly, therefore, breast cancer was detected at a higher frequency in relatives of breast cancer patients, and those detections were at earlier ages than expected. Advantageously, treatment could be instituted earlier than if the cancers had been detected after the onset of symptoms.

Owing to differences of disease occurrence, onset, type, and modification of familial risks by the woman's age and reproductive and medical history, surveillance programs aimed at early detection must be individualized. The appropriate screening procedures, i.e., breast self-examination, breast examination by a health professional or physician, thermography, or mammography, should be utilized in these surveillance programs. How often should depend on the woman's age, prior history of breast cancer, family history of premenopausal or bilateral disease, parity, age at first pregnancy, prior history of benign breast disease, and age at menarche.

There is growing interest in prophylactic mastectomy as a means of primary breast cancer control, particularly by women belonging to high-risk cancer families. This is controversial because women specifically at high risk to the disease cannot as yet be identified by any tumor, biologic, or genetic marker; second, no guides exist outlining what constitutes a family history of sufficient magnitude to justify prophylactic mastectomy; and third, prophylactic subcutaneous mastectomy with implants is itself controversial because of the possibility of an uncertain cosmetic result and the fact that not all breast tissue is removed by the procedure. In spite of the controversy, prophylactic mastectomy should be offered as a cancer control option to high-risk women.

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