**Questions and Answers:**

**Second National Conference on Breast Cancer**

The presentations by participants in the Second National Conference on Breast Cancer held in Los Angeles on May 17, 18 and 19, 1971 included a question and answer period. Because time did not allow all questions to be answered during the conference, the unanswered questions were forwarded to the participants. Their answers are published below.*

Question addressed to

**Joseph H. Farrow, M.D.,**
Memorial Hospital for Cancer and Allied Diseases, New York,
New York:

*Would you ever prescribe estrogens for menopausal symptoms in a patient who has had a mastectomy for cancer?*

**Dr. Farrow**

In general, postmastectomy patients are advised not to take estrogens alone or in combination with other hormones for mental or physical menopausal disturbances. This applies particularly to (1) patients whose carcinoma appeared clinically while taking estrogens or shortly thereafter, (2) those who had a prophylactic castration or a natural menopause within a short time after the breast surgery, (3) patients with a poor prognosis because of a large primary lesion or metastases in multiple axillary lymph nodes and (4) those in whom an excisional biopsy of the opposite breast showed atypical hyperplasias.

Exceptions have been made in a small number of patients with persistent and very distressing menopausal symptoms. The exceptions should be confined to those patients with a good clinical and pathological prognosis and with a disease-free interval of at least three years. The interval should be five or more years in patients with a fair but not a poor prognosis. A thorough physical examination before starting hormonal therapy is important. In addition, there should be mammograms of the remaining breast, X-rays of the chest and, in most cases, of the skeletal system to detect possible asymptomatic, nonpalpable local or distant metastases. Routine follow-up examinations should be done more often in patients taking estrogens. The doses should be small and not given daily during the entire month. They should be discontinued if disturbances or physical changes occur in the remaining breast.

Questions addressed to

**George P. Rosemond, M.D.,**
Temple University, School of Medicine, Philadelphia, Pennsylvania:

*In your opinion, are the factors of strong family history of cancer and increased bilaterality in younger patients sufficient to warrant prophylactic simple mastectomy?*

**Dr. Rosemond**

Although there are a few well-documented "breast cancer families,"
the evidence suggests that unless several close relatives, such as mother and aunts, have had breast cancer, family history is not important. A woman should be considered part of a high-risk group if the mother and one or more aunts have had breast cancer. Anyone in this high-risk group should have routine evaluation by all available methods. Prophylactic mastectomy seems radical based on present evidence except in the unusual event that family incidence had been consistently high for two plus generations. As far as I know, there has been no measurable recent increase in bilateral incidence in young people.

**Is radical mastectomy better than simple mastectomy for minimal breast cancer?**

**Dr. Rosemond**

The purpose of surgery for breast cancer is complete removal of the diseased area. If complete removal can be accomplished by simple mastectomy or total mastectomy, this is sufficient. There is good evidence indicating that about two thirds of all breast cancers are multicentric in the original breast. Anything less than simple or total mastectomy is, therefore, risky. Also, about one third of those patients who have normal nodes as judged by pre-operative (clinical) evaluation do have involved nodes. This great possibility of error has made radical mastectomy a routine procedure for most surgeons. A prospective cooperative study, which should go a long way toward establishing whether radical mastectomy is better than simple mastectomy for minimal breast cancer, is just beginning. As of now, radical mastectomy offers a wider margin for error and is probably the safest 'routine' procedure. In my opinion, simple (total) mastectomy is reasonable in treating certain tumors which rarely metastasize to lymph nodes, for example, cystosarcoma phylloides, or tumors which have an extremely poor prognosis when they do metastasize.

Question addressed to

**Sidney J. Cutler, Sc.D.,**
National Cancer Institute,
Bethesda, Maryland:

*Why can't the increased survival in breast cancer at five years be explained entirely by earlier diagnosis?*

**Dr. Cutler**

There has been an increase in the percentage of breast cancers classified as localized at diagnosis, from 38 percent in the 1940's to 46 percent in 1960-64. However, survival rates have increased within certain stages (i.e., among patients with regional spread of disease and among patients with localized tumors). This may reflect the benefit of better selection of treatment strategies for individual patients as well as improvement in the technical skills of doctors. On the other hand, the improved survival within stage categories may be due to a change in the state of the disease within each broad stage class, e.g., a shift towards smaller tumors within the localized group, and towards less extensive direct spread of the tumor and fewer involved lymph nodes within the regional group.

Whatever the combination of factors that has resulted in improved survival rates, it is noteworthy that patients have truly benefited. The 20-year survival rate, adjusted for normal mortality expectation, provides a meaningful measure of the proportion of successfully treated patients. For patients treated in the 1940's, the adjusted 20-year rate was 30 percent.
Based on the upward shift of survival curves for successive calendar cohorts of patients, the estimated 20-year rate for patients treated in 1960-64 is 39 percent. For surgically treated patients with localized disease the corresponding upward shift is from 56 to 62 percent. (Cutler, S. J., and Heise, H. W.: Long-term end results of treatment of cancer. J. A. M. A. 216:293-297, 1971.)

Question addressed to Calvin Zippin, Sc.D., University of California, Cancer Research Institute, San Francisco, California: What are your criteria for selecting high-risk groups?

Dr. Zippin
One criterion for selecting a high-risk group is to try to identify a group of individuals who will produce a numerically high yield of breast cancer cases. Thus, with the gradient of increasing risk of breast cancer with increasing age, we may choose to select for study or for a program of diagnostic screening, women over a certain age (for example, forty-five years). This group may be expected to yield a sizeable proportion of the estimated 69,000 annual total number of new cases of female breast cancer in the United States. In addition to the relationship with age and other factors such as race and socioeconomic status, breast cancer risk has also been shown to be higher in single women than in married women, in those with a positive family history of breast cancer and in women with a history of prior breast conditions.

Another interesting approach is to try to identify smaller groups of individuals who, although they will not produce large numbers of cases, may be able to shed light on the basic nature of the disease. We may cite breast cancer in Japanese women which is considerably less common than in the overall group of American women. However, among Japanese women there may be subgroups of individuals with relatively high risks. For example, there is the suggestion, based on the work of my colleague, Dr. Nicholas L. Petrakis (Petrakis, N. L.: Cerumen genetics and human breast cancer. Science 173: 347-349, 1971), that the risk of breast cancer may be higher in the small proportion of Japanese women with wet cerumen (earwax) compared with those that have the dry type. This fascinating observation shows potential for helping to piece together metabolic relationships which may play a role in breast carcinogenesis. Thus, although the number of Japanese breast cancer patients may be comparatively low, study of those who do develop the disease may help us to a better understanding of the factors behind the actual disease process.

Question addressed to Herbert B. Taylor, M.D., St. Louis University, School of Medicine, St. Louis, Missouri: What effect does 'the pill' have in cancer of the breast already present?

Dr. Taylor
In some instances, oral contraceptive agents have produced remissions in postmenopausal women with breast cancer. But I think the question refers to the younger woman taking the pill for purposes of contraception who is found to have mammary carcinoma.

Histologically, there are no changes in mammary carcinoma related to oral contraceptive use. Whether the pill will have any effect on prognosis is unknown. Pregnancy is generally accepted as having an adverse influence on breast cancer so there is some cause for concern, but until there is some evidence to the contrary, I don't believe the possible added risk in these women is significant and is not a contraindication to the use of oral contraceptives.
Questions addressed to  
**Mortimer B. Lipsett, M.D.,**  
National Institute of Child Health and  
Human Development, Bethesda,  
Maryland:  
*Do you feel that the serum estrogen level correlates with the state of disease and responds to ablative endocrine therapy?*

**Dr. Lipsett**  
There are no studies of plasma estrogen concentrations and the response to ablative therapy. This would be important in postmenopausal women, although the low levels of estrone and estradiol would make such a study difficult. There is no correlation between urinary estrogen excretion and the response to ablative therapy.

*You stated that the pill contains "small excesses of estrogens." *Does the pill contain estrogens and progestins identical to the human hormones or are those in the pill "abnormal variants"?*

**Dr. Lipsett**  
The oral contraceptives contain synthetic estrogens and progestins which differ chemically from the secreted hormones but have most of the same physiologic effects. Since the oral contraceptives cause increases in several serum proteins, such as ceruloplasmin, alpha-antitrypsin, thyroxine-binding globulin and cortisol binding globulin similar to those increases caused by excessive estrogen administration, it is fair to conclude that the oral contraceptives contain greater than physiologic amounts of estrogen.

Question addressed to  
**Harish C. Chopra, Ph.D.,**  
National Cancer Institute, Bethesda,  
Maryland:  
*Were viral particles present in the opposite breast and in metastases?*

**Dr. Chopra**  
The virus particles were seen in the biopsy material of the other breast. Similarly, virus particles were detected in the metastases of axial lymph nodes.

Question addressed to  
**Edward F. Lewison, M.D.,**  
Johns Hopkins University, Baltimore,  
Maryland:  
*Please comment on prophylactic oophorectomy in premenopausal breast cancer patients.*

**Dr. Lewison**  
Ever since Schinzinger (1889) first proposed oophorectomy as a pro-

phylactic adjunct to the surgical treatment of breast cancer, the value of this procedure in premenopausal patients has remained "the doctor’s dilemma." Because of this area of uncertainty, the National Surgical Adjuvant Breast Project initiated in 1961 a randomized prospective clinical trial to obtain definitive data regarding the value of prophylactic oophorectomy carried out in premenopausal patients as an adjunct to radical mastectomy. This report appeared recently in *Surgery, Gynecology and Obstetrics* 131: 1055-1064, 1970.

Reliable data available at the end of three, four and five years indicated no significant difference in survival or recurrence rate between patients having prophylactic oophorectomy and those not having prophylactic oophorectomy. No evidence existed in any of the subgroups indicating any benefit to be derived from prophylactic oophorectomy in the treatment of the premenopausal patient with operable breast cancer.

Question addressed to  
**Harish C. Chopra, Ph.D.,**  
National Cancer Institute, Bethesda,  
Maryland:  
*What histologic type of human breast cancer corresponds to your monkey tumor and what is the incidence of breast cancer in Rhesus monkeys?*

**Dr. Chopra**  
Histopathological examination of the breast tumor biopsies in our study showed that the viable portions
resembled a mammary adenocarcinoma of highly undifferentiated type which is very rare in humans. There are very few reported cases of breast cancer in Rhesus monkeys.

Question addressed to
Dan H. Moore, Ph.D.,
Institute for Medical Research,
Camden, New Jersey:
Has the RNA instructed DNA polymerase been identified in American breast cancer material?

Dr. Moore
RNA dependent DNA polymerase has been found in human milk particles having density 1.175-1.185 which is the density of most mouse virions. Milks without these particles failed to show the polymerase (Sholm, J.; Spiegelman, S., and Moore, D.: RNA-dependent DNA polymerase activity in virus-like particles isolated from human milk. Nature 231: 97-100, 1971). As yet it is impossible to interpret the meaning of polymerase in mammary tumor tissue. Only reverse transcriptase from isolated virus which is dependent on the viral RNA has significance. The polymerase has been found in both American and Parsi milks.

Question addressed to
William F. Feller, M.D., Ph.D.,
Georgetown University Hospital,
Washington, D.C.:
Have virus-like particles been seen in other body fluids or in any tissues of the female with cancer?

Dr. Feller
Virus-like particles have been seen in primary tissue culture explants of human breast cancer cells.

Question addressed to
Gabriel Seman, M.D.
The University of Texas M.D.
Anderson Hospital and Tumor Institute,
at Houston:
How successful is breast cancer tissue culture and how long does it last?

Dr. Seman
Generally, it is not difficult to start primary monolayer cultures of human breast tumors by trypsinization or by mincing alone, if the tumor tissue is not too fibrous or fatty. Primary cultures are even easier to set up from pleural effusions, sometimes just by putting effusion fluid, after it has clotted, in tissue culture flasks. About 50 percent of the cultures derived from breast tumors and 90 percent of those derived from pleural effusions of breast cancer patients have been subcultured more than once. Most of the cultures tend to enter a stationary phase after a varying number of passages, somewhere between 150-300 days. A few of them have been maintained over a year. Chances of establishing monolayer cultures of breast tumors and pleural effusions from breast cancer patients are apparently low. It is not known whether the successful cultures were cultures of cancer cells.

Please explain the change of morphology in tissue culture.

Dr. Seman
Morphology of a monolayer tissue culture is complex. Its definition is complicated by the fact that cells in long term cultures usually lose many of the specific characteristics they had in their site of origin. However, it is generally possible to distinguish an epithelial culture from a fibroblastic, or lymphoblastoid, etc., culture because the cells have a morphology directly related to their nature (often confirmed by cytochemical procedures) and also grow according to a characteristic pattern. Using similar procedures to prepare and to grow cultures from breast tumors and pleural effusions, the cultures derived from each of these two sources have strikingly similar
morphologies, although the true nature of the cells has still not been clearly established. On the other hand, it is well known that variations in culturing conditions (medium, temperature, substrate, etc.) may drastically change the morphology and the growth pattern of the cells. For instance, pleural effusion cells look completely different when grown on plastic or when grown on fibrin clot. The number of cells seeded in a subculture may by itself determine the growth pattern and the morphology of the cells until the next subculture. It is, therefore, important, when comparing cultures and trying to classify them, to do it in well-established conditions of maintenance.

Questions addressed to

Thomas H. M. Stewart, M.B., Ch.B.,
University of Ottawa, Ottawa, Ontario, Canada:

Doesn't the fact that there is no cross reactivity among the patients negate the idea of a common etiological factor?

Dr. Stewart

I have indeed shown cross reactivity in half the patients tested with allogenic extracts so this would suggest that they shared common antigens. One might speculate that there is a shared aetiologic factor.

Have you any controls, i.e., percent of positive skin test in patients to their normal breast tissue extracts?

Dr. Stewart

We have used autologous white cells as a source of nucleated control cells in all cases; in only one patient who had a positive tumor reaction was there a reaction to her own white cells. She had circulating t.e. cells and thus may have had lupus erythematosus. Such patients are thought to be hyperreactive on skin testing. We have not used residual breast tissue as controls since we felt it would be impossible to exclude small foci of carcinoma. The uninvolved breast tissue was not used for ethical reasons.

Question addressed to

H. Stephen Gallager, M.D.,
The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston:

If multicentric cancer is so high in the same breast and in the opposite breast of cancer patients, why is bilaterality of clinical cancer so low?

Dr. Gallager

This apparent discrepancy has multiple causes. The time required for the progression of intraepithelial neoplasia to a palpable mass is unknown, but is unquestionably long—a matter of years. Since most breast cancers are currently discovered relatively late in life, and since little more than half the patients survive five years, the probability is great that death, either as a result of the original carcinoma or as a result of an intercurrent disease, will occur before a second primary has had time to become clinically evident.

Another factor which has heretofore minimized the significance of the second primary is that differentiation from metastasis is difficult. In a patient who has had one mastectomy, the appearance of a new mass in a remaining breast is likely to be considered evidence of metastasis. There are, unfortunately, no reliable criteria, either clinical or mammo-graphic, for distinguishing between primary and metastatic breast masses. Even histologic demonstration of accompanying noninvasive carcinoma is only presumptive evidence that the second mass is a new primary lesion.
The importance of the dilemma of the second breast can be expected to increase as methods of early detection improve. Among patients who are effectively treated for initial minimal carcinomas, long survivals will be more frequent, and thus there will be more available time for the evolution of second primaries. The urgent question is not whether bilaterality is a statistically significant phenomenon, but how this problem can best be managed. To this question, there is as yet no authoritative answer.

Questions addressed to

Luciano Ozzello, M.D.,
Michael Reese Hospital and Medical Center, Chicago, Illinois:
Would you comment on the fact that cytoplasmic processes identical to those shown in your pictures have been described in endothelium of granulation tissue capillaries which is not precisely an invasive lesion?

Dr. Ozzello

Cytoplasmic protrusions through gaps in basal laminae are not unique to malignant cells. They have been seen in endothelium of granulation tissue capillaries, of peripheral capillaries in experimental nephritic edema, of glomerular capillaries in severe nephritides, of venules in mammary dysplasia and in normal pituitary epithelium. In these conditions the cytoplasmic protrusions are not followed by further "invasion" of the adjacent stroma and are presumably retracted or destroyed. It is possible, although direct proof is lacking, that some of the cytoplasmic protrusions of mammary carcinoma cells are still reversible. Nevertheless, in carcinoma of the breast, as well as in some experimental epidermal tumors, it is possible to envision progressive steps ranging from the appearance of minute cytoplasmic protrusions to the formation of separate nests of invasive cells indicating that some, if not all, of the cytoplasmic protrusions demonstrable ultrastructurally in intraductal carcinomas and lobular carcinomas in situ do progress into irreversible stromal invasion.

What are the absolute criteria of cancer in situ in the light microscope?

Dr. Ozzello

It is common practice to designate a carcinoma of the breast as in situ when no stromal invasion can be demonstrated by diligent light microscopic study. It is important to remember, however, that metastases can occur in patients with ductal and, less frequently, lobular carcinomas in which no invasion could be documented by histologic examination. The inadequacy of the currently available histological techniques is further highlighted by the observation that foci of invasion too small to be resolved by light optics can be seen with the electron microscope. Consequently, a light microscopic diagnosis of in situ carcinoma of the breast should be interpreted to mean that stromal invasion could be neither demonstrated nor ruled out in the tissue examined.
Question addressed to

John E. Martin, M.D.,
St. Joseph's Hospital, Houston,
Texas:

How do you localize the biopsy areas for the surgeon in cases with minimal radiographic findings? How do you verify the adequacy of the biopsy? Does the resultant intramammary scar confuse subsequent mammogram interpretations?

Dr. Martin

In many patients having serial examinations of the breast, we have found minimally invasive carcinoma with lesions measuring as small as 2-3 mms. in diameter. Localization of these lesions has not proved to be difficult. The quadrant of the breast is usually localized without difficulty and the level within this quadrant whether near the areola or deep is specified. A wedge resection of this quadrant is usually done and X-ray examination of the specimen is used to localize the area for histological study. Most of these lesions are found on the frozen sections at that time. Occasionally, the neoplasm is not demonstrated until the final sections are seen. The resultant mammary scar does not usually confuse subsequent mammographic interpretations.

Does microcalcification in a breast mammogram with some density indicate a cancer?

Dr. Martin

Solitary areas of localized microcalcifications with associated density usually indicate a carcinoma. Multiple grouped areas of micro-califications with associated density throughout the breast usually indicate sclerosing adenosis.

How often should serial mammograms be performed in the high-risk patients?

Dr. Martin

Many patients considered to be in high-risk groups have serial examination of the breast at six-month to yearly intervals depending upon the severity of the breast disease. For example, a patient having had a radical of one breast is examined at six-month intervals for a period of three to four years.

In Step

The natural scientist is often faced with a series of observations, a set of phenomena, into which he attempts subsequently to introduce some sort of chronological or causal order. . . . Whatever he does, there remains much darkness between the points of light. Whether he emphasizes the light or dwells on the obscurities will depend upon his temperament, but even more upon the temper of the times . . . which acts as a censor forbidding him to be ahead by more than one or two steps. If he runs too fast, he disappears from our sight; if he goes too slowly, he joins the 18th Century. For most people, this is not a problem: they are where all the others are—Erwin Chargaff, On Some Biological Consequences of Base-pairing in the Nucleic Acids. In: Developmental and Metabolic Control Mechanisms and Neoplasia. Baltimore: Williams and Wilkins, 1965. P. 7.