3. Braunstein GD, Rasor J, Wade ME: Presence in normal human testes of a chorionic-gonadotropin-like substance distinct from human luteinizing hormone. N Engl J Med 293:1339-1343, 1975
4. Chen H-C, Hodgen GT, Matsuura S, et al: Evidence for a gonadotropin from nonpregnant subjects that has physical, immunological, and biological similarities to human chorionic gonadotropin. Proc Natl Acad Sci USA 73:2885-2889, 1976
5. Yoshimoto Y, Wolfsen AR, Odell WD: Human chorionic gonadotropin-like substance in nonendocrine tissues of normal subjects. Science 197:575-576, 1977
6. Richert ND, Bramley TA, Ryan RJ: Hormone binding, proteases and the regulation of adenylate cyclase activity, Novel Aspects of Reproductive Physiology. Edited by CH Spilman, JW Wilks. New York, SP Medical and Scientific Books, 1978, pp 81-106
7. Anderson T, Waldmann TA, Javadpour N, et al: Testicular germ-cell neoplasms: recent advances in diagnosis and therapy. Ann Intern Med 90:373-385, 1979
8. Lange PH, McIntire KR, Waldman TA, et al: Serum alpha fetoprotein and human chorionic gonadotropin in the diagnosis and management of nonseminomatous germ-cell testicular cancer. N Engl J Med 295:1237-1240, 1976
9. Waldmann TA, McIntire KR: The use of a radioimmunoassay for alphafetoprotein in the diagnosis of malignancy. Cancer 34:1510-1515, 1974
10. Hansen HJ, Snyder JJ, Miller E, et al: Carcinoembryonic antigen (CEA) assay: a laboratory adjunct in the diagnosis and management of cancer. Hum Pathol 5:139-147, 1974

## A NEW EUROPEAN EDITION

When our name was changed from the *Boston Medical and Surgical Journal* to the *New England Journal of Medicine* in 1928, it was in recognition of the fact that our orbit had by then extended well beyond the city of our birth. Although the *Journal* had become national by most standards, it seemed at the time unnecessary, even extravagant, to assert titular identification with regions west of the Hudson or east of Maine because we still drew most of our subscribers from the northeastern corner of the United States.

But that was over half a century ago, and our horizons have expanded considerably since then. We now claim international scope. Of our current circulation of nearly 200,000, more than 16 per cent is outside the United States. (Approximately the same fraction of all the manuscripts and letters that we receive comes from foreign contributors.) Overseas subscriptions, particularly in Europe, are among the fastest growing components of our circulation. European subscribers totaled just over 8000 in 1973, but the figure has more than doubled since then. This increase undoubtedly stemmed in part from our efforts to distribute the *Journal* more efficiently in Europe. In 1973, we began to print a European edition in London and mail it from there to the rest of Great Britain and to the Continent, Africa and the Near East. However, in 1975, after our London printer went out of business, we arranged to have the European edition printed in Hanover, New Hampshire, trucked to Boston and then flown to Amsterdam, where it was mailed to individual subscribers.

That system, although costly, worked well. During 1975-1976 when I lived in Oxford, England, I regularly received my European edition on Thursday mornings, often a day or two before the regular American edition was being delivered to my office back home. But the mounting costs of this arrangement soon forced us to consider other alternatives.

Beginning with the first (July 5th) issue of Volume 301, our European edition is again being printed and mailed in England. Negatives of our pages are prepared here in Boston, flown each week to London, printed in Maidstone (Kent) by the firm of Alabaster Passmore and Sons and then wrapped and mailed by R. L. Polk and Company in Sudbury (Suffolk). This latest version of our European edition is streamlined and almost entirely shorn of advertisements. It is printed on light but good-quality paper that does not compromise the clarity of illustrations. It weighs a svelte three ounces, as compared with the 10 or 11 ounces of its bloated and glossy American counterpart. Its cover of unrelieved black and white seems a bit somber without the traditional red trimming, but the new European edition is otherwise a complete and bona fide *New England Journal of Medicine,* lacking nothing of substance, even down to Notices and Corrections.

We hope that the new arrangement will enable us to deliver the *Journal* to our European readers each week on schedule, and we hope that they will continue to find its contents worth reading. We value our overseas friends and shall continue to be responsive to their interests.

Arnold S. Relman, M.D.

# SOUNDING BOARD

## BREAST-CANCER MANAGEMENT

### Alternatives to Radical Mastectomy

The conclusions of the NIH consensus meeting on "The Treatment of Primary Breast Cancer" published in this issue of the *Journal,* deserve more consideration than mere acceptance or rejection depending on whether they support one's personal point of view. The report does not indicate the reasons for the conclusions, and they undoubtedly differed among the participants. I was a participant, and I should like to present my reasons for the recommendations and some personal thoughts about the meaning of the report.

The recommendations that total mastectomy and axillary dissection should replace the Halsted radical mastectomy as the current treatment standard and that the evaluation of procedures aimed at preserving the breast should be vigorously pursued were not arbitrary ones. They emerged from the results of investigations that have culminated in a new conception of the biology of breast cancer.

Disagreement about the surgical management of breast cancer is related to differences in perception of the biology of the disease, particularly in terms of tumor spread. Two divergent hypotheses of tumor biology are at the heart of the disagreement. The

hypothesis that motivated Halsted holds that: the bloodstream is of little importance as a route of metastasis; tumor cells traverse lymphatics by direct extension; a growing tumor remains localized at its site of origin, spreads to regional lymph nodes and then systemically in an orderly defined manner; regional lymph nodes provide an effective barrier to the passage of tumor cells; and a tumor is autonomous of its host.[1] If one accepts this hypothesis, the therapeutic approach taken must of necessity differ from the approach taken by the investigator who accepts the alternative hypothesis, which is that cancer is a systemic disease involving a complex spectrum of host–tumor interrelations and that variations in local–regional therapy are unlikely to affect survival substantially.

I have participated during the past two decades in many of the laboratory and clinical studies that contributed to the formulation of an alternative hypothesis that challenges halstedian principles of surgery and to the conclusions of the NIH consensus report. The following is a brief summary of some of these studies.

My colleagues and I have demonstrated that regional lymph nodes are not a barrier to the dissemination of tumor cells[2]; have indicated the biologic importance of these nodes and have shown that there are biologic, rather than anatomic, reasons why certain nodes in patients with cancer contain metastases while others do not.[3] We have shown that tumor cells in the bloodstream enter the lymphatics and vice versa, an observation that indicates that the blood and lymphatics form a unified system in terms of tumor-cell dissemination.[4] Those findings led us to conclude that there is no orderly pattern of tumor-cell dissemination that could be based on mechanical considerations. Studies first undertaken in 1958 indicated that host factors are important in the development of metastases and that a tumor is not autonomous of its host.[5] The presence of dormant tumor cells was demonstrated, and it was shown that perturbation of the host could produce lethal metastases from those cells.[6] We subsequently believed that breast cancer is a systemic disease — probably from its inception. That statement never implied that overt metastases will develop in all persons at some time; nor does it imply that only those with metastases represent the population with disseminated disease. The first clinical trial of the National Surgical Adjuvant Breast and Bowel Project (NSABP) showed that an inordinately high proportion of patients become treatment failures within 10 years after "curative" operations, a finding that lends support to the concept that clinical breast cancer is a systemic disease.[7] On the basis of these and other findings, the hypothesis was formulated that the regional lymph node is an indicator of host–tumor relations. The lymph node that contains tumor cells is a reflection of an interrelation that permits the development of metastases rather than being an instigator of distant disease. Clinical trials conducted by the NSABP indicated that the number of axillary nodes containing tumor cells is an important prognostic variable.[8] These trials also showed that recurrence and survival of more than 2000 patients studied by the NSABP were independent of the number of axillary nodes removed and examined.[9] Patients with five to 10 nodes that were free of tumor cells showed recurrence and survival rates similar to those in patients with 25 to 30 nodes free of tumor. Conversely, patients with two of five nodes positive for tumor were at the same risk as those with two of 30 nodes positive. Those observations raised questions concerning the virtue of the "halstedian-type" axillary dissection.

In August, 1971, members of the NSABP undertook a prospective randomized clinical trial to confirm or deny the halstedian principles of cancer surgery. The results of that trial, which involved more than 1700 women, indicate[10] that in patients without clinical evidence of node involvement (40 per cent of whom had histologically positive nodes), three distinctly different treatment regimens — radical mastectomy, total (simple) mastectomy and local–regional irradiation or total mastectomy and removal of nodes that later became clinically positive — yielded no substantial difference in the overall incidence of treatment failure, the incidence of distant metastases or survival. Similarly, in patients with clinical evidence of node involvement, treatment by radical mastectomy or total mastectomy and local–regional irradiation yielded no substantial difference on the basis of the aforementioned criteria. Since the findings do not support the efficacy of the en-bloc dissection (the keystone of the halstedian principles of tumor management) and fail to demonstrate either a benefit or disadvantage for the removal of axillary nodes in incidence of distant metastases or survival, they refute halstedian principles and strengthen the credibility of the hypothesis. Thus, by repudiating the radical mastectomy, the consensus statement, wittingly or unwittingly, also rejects the principles that had provided the scientific basis for the operation. For that reason, if for no other, the report is of singular importance in the annals of oncology.

Total mastectomy and axillary dissection, as recommended in the consensus report, are not synonymous with a modified radical mastectomy. The term "modified radical mastectomy" is not descriptive or accurate, and therefore should not be employed. This is particularly true since axillary dissection, in conjunction with either total or segmental mastectomy, is for patient-staging purposes and is therapeutic only in that it reduces the possibility of subsequent regional recurrences. It does not alter the incidence of systemic recurrence or patient survival.

The negation of the radical mastectomy and the principles on which it is based has eliminated most of the biologic considerations that might contraindicate the performance of breast-conserving operations. The phenomenon of tumor multicentricity, however, remains to be considered.[11] Sound justification exists for a clinical test of the hypothesis that multicentricity is not a deterrent to the performance of operations that

preserve the breast. Despite the substantial incidence of multifocal lesions in both breasts of women with cancer, only rarely is there evidence of two or more overt cancers in the same breast, synchronous bilateral tumors are uncommon, and the incidence of an asynchronous primary tumor in the uninvolved breast fails by far to approach the incidence of occult lesions detected by random biopsy or at autopsy. All cancers do not progress to overt lesions; other solid tumors have been detected by pathological means with much greater frequency than they are seen clinically. Differences in opinion regarding the importance of multicentricity have evoked controversy about segmental mastectomy. That basic biologic issue cannot be resolved by "populism" or emotional trends. By applying the scientific method for clinical problem solving, the NSABP is conducting the only prospective, randomized controlled clinical trial in the United States and Canada to evaluate the efficacy of segmental mastectomy in conjunction with axillary dissection. It is the only clinical trial evaluating the biologic importance of tumor multicentricity. To accomplish this goal, women who have undergone segmental mastectomies are divided into two groups — one will receive breast irradiation, and the other will not. No published data have indicated that breast irradiation is necessary or even desirable in all patients. Although 400 women have already entered the trial, considerably larger numbers are needed to obtain credible data. Surgeons are invited to participate in what this investigator believes is the most important trial on breast cancer ever conducted since it may demonstrate that breast removal is not necessary in all patients. Interested persons can obtain further information from the NSABP.

From this overview, it is apparent that therapeutic strategies for breast cancer have evolved over time in stepwise fashion and have resulted from a better understanding of the biology of the disease. It is logical to anticipate that this course of events will continue. Consequently, the present posture, like the preceding ones, must be considered provisional.

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## REFERENCES

1. Fisher B: The surgical dilemma in the primary therapy of invasive breast cancer: a critical appraisal. Curr Probl Surg October, 1970, pp 1-53
2. Fisher B, Fisher ER: Transmigration of lymph nodes by tumor cells. Science 152:1397-1398, 1966
3. Fisher B, Saffer EA, Fisher ER: Studies concerning the regional lymph node in cancer. VII. Thymidine uptake by cells from nodes of breast cancer patients relative to axillary location and histopathologic discriminants. Cancer 33:271-279, 1974
4. Fisher B, Fisher ER: The interrelationship of hematogenous and lymphatic tumor cell dissemination. Surg Gynecol Obstet 122:791-798, 1966
5. Fisher ER, Fisher B: Host influence on tumor growth and dissemination, The Biological Basis of Radiation Therapy. Edited by E Emanuel, MD Schwartz. Philadelphia, JB Lippincott Company, 1966, pp 484-517
6. Fisher B, Fisher ER: Experimental evidence in support of the dormant tumor cell. Science 130:918-919, 1959
7. Fisher B, Slack N, Katrych D: Ten year follow-up results of patients with carcinoma of the breast in a co-operative clinical trial evaluating surgical adjuvant chemotherapy. Surg Gynecol Obstet 140:528-534, 1975
8. Fisher B, Ravdin RG, Ausman RK, et al: Surgical adjuvant chemotherapy in cancer of the breast: results of a decade of cooperative investigation. Ann Surg 168:337-356, 1968
9. Fisher B, Slack NH: Number of lymph nodes examined and the prognosis of breast carcinoma. Surg Gynecol Obstet 131:79-88, 1970
10. Progress Report of the Sixteenth Semi-annual Meeting of the National Surgical Adjuvant Project for Breast and Bowel Cancers (NSABP), Spring Meeting, Tucson, Arizona, March 28-31, 1979
11. Fisher ER, Gregoria R, Redmond C, et al: Pathologic findings from the National Surgical Adjuvant Breast Project (Protocol No. 4). I. Observations concerning the multicentricity of mammary cancer. Cancer 35:247-254, 1975

# CORRESPONDENCE

Letters to the Editor are welcomed and will be published, if found suitable, as space permits. They must be signed, typewritten in double spacing (including references), submitted in duplicate, must not exceed 1½ pages in length and will be subject to editing and possible abridgment. To be considered for publication, letters referring to a recent *Journal* article should be received within six weeks of the article's publication date.

## 5-FLUOROURACIL FOR GASTROINTESTINAL CANCER

*To the Editor:* We would like to question the negativism of Dr. Moertel's recent review of gastrointestinal-cancer chemotherapy,[1] in which he denigrated his own early work[2] and that of the Wisconsin group.[3] His statement that 5-fluorouracil "occasionally" produces transient tumor regression is contradicted by his concession that the drug produces responses in "only about 15 to 20 per cent" of patients.

The proportion of responses can be doubled by use of an optimum dosage schedule developed 22 years ago. In a long-term randomized study by the Central Oncology Group,[4] regression rates of 33 to 38 per cent resulted from a three-phase 5-fluorouracil regimen consisting of a loading course, titration to mild toxicity (adjusted on Days 10 to 17 according to the patient's tolerance) and sustained weekly maintenance therapy thereafter. Three other dose regimens yielded only 12 to 18 per cent responses. The study verified Moertel's early observation that lower response rates should be expected whenever no toxicity or severe toxicity is induced.[3] The three-phase 5-fluorouracil regimen is flexible — a characteristic that, unfortunately, makes it unsuitable for the usual rigid protocol schedules employed worldwide. This may account for the otherwise inexplicable conclusion of Schein's group[5] that the better results obtained with the three-phase regimen "are not generally applicable."

The review also incorrectly stated that 5-fluorouracil has no worthwhile effect on survival. Moertel, however, showed in a double-blind study[6] that a single loading course (40 mg per kilogram of body weight) prolonged survival for four months in patients with pancreatic cancer, 5.5 months in patients with colorectal cancer and 8.5 months in patients with gastric cancers also treated with radiotherapy. Moertel quoted Higgins et al.[7] as indicating in 1976 that there "seems little reason to continue studies using 5-fluorouracil as a single agent," yet in 1978 Higgins et al. reported that all five Veterans Administration studies showed reason for its use as an adjuvant.

We do not see any reason why 5-fluorouracil, properly titrated, should not be employed as a standard clinical treatment for cancer. Perhaps as many as 30,000 patients among the 100,000 with gastrointestinal cancer could live for an additional six months at small cost and inconvenience. We believe that few patients would willingly forgo this chance.

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