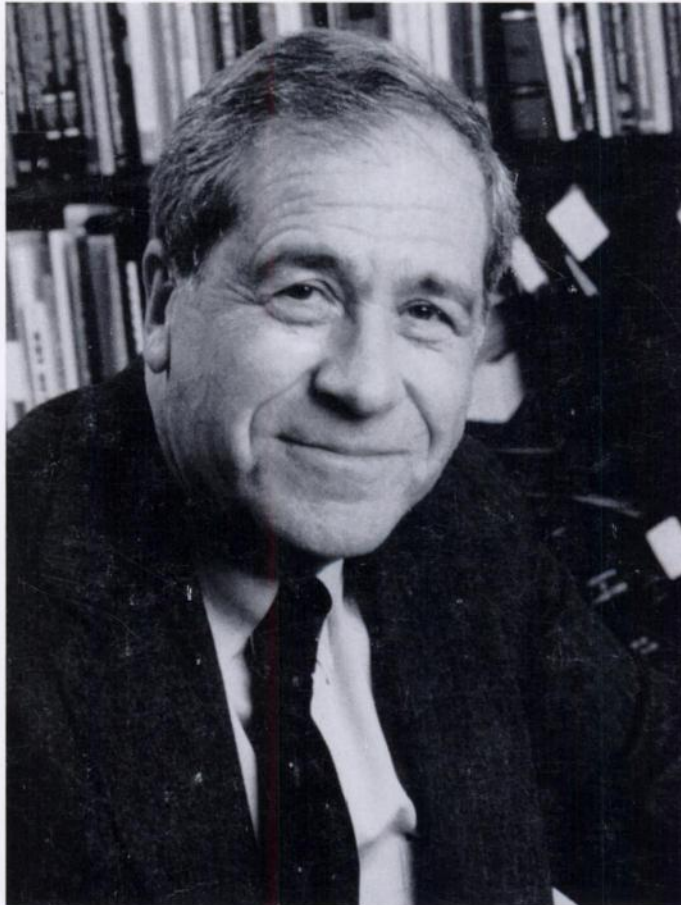




Cancer Research

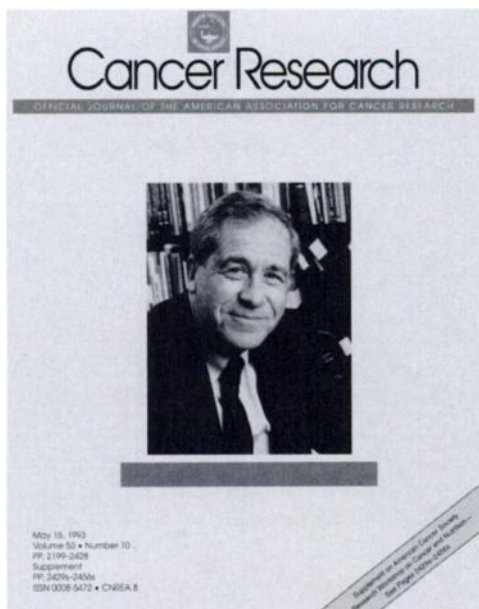
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COVER LEGEND



This issue's cover features Dr. Bernard Fisher, who is sharing the Sixteenth Annual Bristol-Myers Squibb Award for Distinguished Achievement in Cancer Research with Gianni Bonadonna of the Istituto Nazionale Tumori, Milan, Italy.

Research conducted since 1957 by Dr. Bernard Fisher has given rise to a new perception of the phenomenon of tumor metastasis. The results of his laboratory and clinical investigations on metastases led him to formulate, in 1968, a hypothesis of tumor biology different from the anatomical one proposed by William Halsted that had served as the basis for cancer treatment for 100 years. Since 1970, using human breast cancer as the model, Dr. Fisher has used clinical trials to confirm his alternative hypothesis. His findings during the past 15 years have provided new information regarding the natural history of breast cancer and have contributed to a reassessment of the principles of cancer management, particularly as they relate to surgery and systemic adjuvant chemotherapy.

Dr. Fisher challenged Virchow's hypothesis that regional lymph nodes (RLNs) are barriers to tumor cell dissemination, and he was the first to demonstrate that tumor cells traverse RLNs and gain access to efferent lymph or to the blood via lymphatic venous communications within nodes. His finding that tumor cells in portal blood rapidly appear in liver lymph provided the first evidence that tumor cells in blood enter the lymphatic system. He demonstrated that such cells do not necessarily lodge in the capillary bed of the first organ they encounter during their dissemination and concluded, as a consequence, that there is no orderly pattern of tumor cell dissemination related to anatomical considerations, a departure from the concept that had provided the rationale for treatment of solid tumors up to that time.

For more than a decade, Dr. Fisher investigated the relationship between host factors and the development of metastases. He repudiated the concept that a cancer was autonomous of its host, a theory that had been widely accepted until the late 1950s. His studies were instrumental in reinforcing the concept that solid tumors, such as those resulting from breast cancer, are systemic from their inception and that the disseminated cancer cells may represent potential metastases during the life of the host. In 1959, he presented the first experimental evidence to support this hypothesis when he demonstrated that "dormant" tumor cells exist and that, under appropriate host perturbation, they can result in lethal metastases.

Dr. Fisher also examined the role of the RLN in the initiation and maintenance of tumor immunity and found that there are biological rather than anatomical reasons why some nodes contain metastases and others do not. As a tenet of his alternative hypothesis, Dr. Fisher proposed that, contrary to Halstedian concepts, variations in local-regional therapy are unlikely to substantially affect survival.

Two important clinical trials conducted by Dr. Fisher and his associates since 1970 convincingly support the alternative hypothesis he proposed. Findings from these two prospective randomized clinical trials justify breast-preserving surgery and replacement of the Halstedian paradigm for cancer management with one that is biological in concept. The first trial demonstrated that, after 15 years, there was

no significant difference in the rates of disease-free survival, distant disease-free survival, or survival of patients treated by conventional radical mastectomy, total "simple" mastectomy without axillary dissection but with postoperative breast irradiation, or total mastectomy alone and no irradiation followed by axillary dissection only in patients who subsequently developed positive axillary nodes. The second trial, conducted as a result of preliminary observations from the first, has shown, after 10 years of follow-up, that lumpectomy plus breast irradiation and axillary dissection preserves the breast in more than 90% of patients thus treated, with no deleterious effects on distant disease-free survival. As a result of these findings, a National Cancer Institute consensus panel in 1990 indicated that breast preservation is the recommended treatment for women with stage I and II breast cancer.

Dr. Fisher's 1989 publications in the *New England Journal of Medicine* were responsible for altering the management of node-negative breast cancer patients. They indicated the value of chemotherapy for women with estrogen receptor-negative tumors and tamoxifen for women with estrogen receptor-positive tumors. In 1990, he demonstrated that tamoxifen plus chemotherapy is better than tamoxifen alone for the treatment of node-positive breast cancer patients. He is now evaluating the worth of preoperative therapy in a study the results of which could alter the current approach to breast cancer therapy.

Under Dr. Fisher's direction, the first women's health trial to evaluate the use of a preventive agent (tamoxifen) for breast cancer has been initiated in normal women at increased risk for the disease. This trial will also evaluate the use of tamoxifen for the prevention of coronary artery disease and for osteoporosis. The study involves 16,000 women from over 100 institutions in the United States and Canada. This undertaking is viewed as the culmination of Dr. Fisher's three decades of research in the biology and treatment of breast cancer.

Dr. Fisher is a graduate of the University of Pittsburgh, from which he received both the B.S. degree and the M.D. He completed his postgraduate training at this institution, as well as at the Harrison Department of Surgical Research of the University of Pennsylvania, and at the Post-Graduate Medical School of Hammersmith Hospital in London, England.

Dr. Fisher subsequently joined the Faculty of Medicine at the University of Pittsburgh and was appointed Professor of Surgery in 1959. In 1986, he was appointed Distinguished Service Professor. Dr. Fisher is currently the Senior Scientific Director for Clinical Affairs of the University of Pittsburgh School of Medicine and the Scientific Director of the Comprehensive Breast Care Center of the Pittsburgh Cancer Institute.

His many honors and awards include: the Albert Lasker Research Award; the Karnofsky Award of the American Society of Clinical Oncology (ASCO); the Lucy Wortham James Clinical Research Award from the Society of Surgical Oncology; the American Cancer Society Medal of Honor; the Heath Memorial Award of the M. D. Anderson Hospital and Tumor Institute; the degree of Doctor of Science, *Honoris Causa*, from Mount Sinai School of Medicine, City University of New York; the Hammer Cancer Prize; the Susan G. Komen Foundation Tiffany Award of Scientific Distinction; the Philip S. Hench Distinguished Alumnus Award and the Mellon Lecture Award from the University of Pittsburgh; and the Milken Family Medical Foundation Cancer Research Award.

In 1989, the University of Pittsburgh established the annual Bernard Fisher Lecture. In the same year, the ICI Pharmaceuticals Group and the University of Pittsburgh established the Bernard Fisher-ICI Professorship in Surgery. Recently, the University of Pittsburgh awarded him the 1992 Chancellor's Distinguished Research Award. In 1992, Dr. Fisher also received the Durham, North Carolina City of Medicine Award for "extraordinary contributions in the field of medicine in the public interest"; the National Health Council's National Medical Research Award for his pioneering studies in basic and clinical cancer research and especially for his challenge of transitional treatments for breast cancer; the inaugural Brinker International Breast Cancer Award for "his visionary leadership of the National Surgical Adjuvant Breast and Bowel Project and for his sustained contributions to improve primary breast cancer treatment"; and the Dr. Josef Steiner Cancer Research Prize, presented by the University of Bern, Bern, Switzerland, in honor of those who have contributed to the basic knowledge of cancer by their systematic research work with new diagnostic or therapeutic approaches and preventive methods.

Dr. Fisher is President of ASCO, and he is a member of the Institute of Medicine of the National Academy of Sciences and many other scientific societies. He has served on the Board of Directors of ASCO and the American Association for Cancer Research. He currently serves on the editorial boards of numerous nationally known scientific journals and has published more than 470 articles.

Sidney Weinhouse