

HISTORY

of the **NSABP**

PART ONE: The Pre-Pittsburgh Era 1957-1969



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Chairman (1967-1994)
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On April 4 1958, the first patient was enrolled in the first randomized clinical trial designed to determine the worth of systemic adjuvant therapy for primary operable breast cancer. Neither I nor any of the other 22 surgeons who represented the 23 participating institutions in the United States, could have foreseen that, 40 years later, a celebration would honor the origin of the group that subsequently became known as the National Surgical Adjuvant Breast and Bowel Project—the NSABP. None of us could have predicted the longevity of this organization or the magnitude of its impact on the understanding and treatment of breast cancer in the four decades that followed.

In acknowledgement of its 40th anniversary, I have been asked to write a brief history of the NSABP. The history of that organization is more than a description of its administrative structure, a chronology of the clinical trials conducted, or a listing of the data obtained and papers published. It is about the dynamics of the interaction among numerous individuals within the group and among the government and university officials, the public, and pharmaceutical companies. It is not only the story of what was done but also of why it was done, and it is about “political science” as well as basic and clinical science. It is about the women and physicians who participated in the studies. And it is about those who were opposed to the studies and about the role of the medical and lay press. But, most of all, it is about the “culture” of a community of people who were passionate about what they were doing. It is a story that can be told only by those who lived it, reacted to it, remember it, and can record it with probity.

The Original Focus: The NSABP originated in 1957, when the National Institutes of Health (NIH) Cancer Chemotherapy National Service Center (CCNSC) sponsored a program called the Surgical Adjuvant Chemotherapy Projects to test the effectiveness of various anticancer drugs used with cancer surgery. The rationale for that undertaking resulted from clinical and laboratory findings during the 1950s, which suggested that systemic agents given during and shortly after “curative” operations might improve the outcome of cancer patients. There was evidence that 1) tumor cells were dislodged into the blood stream of patients during surgery, thus making an otherwise “perfect” procedure less effective; 2) the growth of cancer cells injected into animal blood could be impaired by the inoculation of chemotherapy; and 3) thiotepa (TSPA) and several other agents might be effective against cancer that had already become established. The CCNSC program received its initial impetus from four individuals, three of whom were surgeons: my mentor, I.S. Ravdin, chairman of the Department of Surgery at the University of Pennsylvania; Warren Cole, chairman of the Department of Surgery at the University of Illinois; George E. Moore, chief of surgery and director of Roswell Park Memorial Institute; and Michael B. Shimkin, of the NIH.

Five organ-site projects, each chaired by a surgeon, were simultaneously instituted by the CCNSC. These projects tested the effectiveness of the TSPA as an adjuvant to excisional therapy for cancer at certain organ sites, i.e., the breast, stomach, colon, and rectum; the efficacy of nitrogen mustard in lung cancer; and the worth of chlorambucil in ovarian cancer. As chairman of the CCNSC Clinical Studies Panel, Dr. Ravdin was head of the Surgical Adjuvant Chemotherapy Projects. Dr. Moore was general chairman of these projects and had administrative responsibility for their activities. Dr. Rudolf J. Noer, chair of the Department of Surgery at the University of Louisville, was the first chairman of the Surgical Adjuvant Chemotherapy Breast Group, which was headquartered at Roswell Park Cancer Institute in Buffalo, New York, where Dr. John Pickren, the first study pathologist, and Mr. R. B. Stiver, project statistician, were also located. Each of the other organ-site programs had a separate organizational plan and headquarters office. None of them continued to function for more than a few years.

In the spring of 1957, 23 surgeons were invited by Dr. Ravdin to attend a meeting at Stone House on the NIH campus to discuss the creation of the

Surgical Adjuvant Chemotherapy Breast Project, which had as its goal the conduct of clinical trials. [I am the only one of the 23 original principal investigators who is still an NSABP member. Four of the original institutions continue to maintain an affiliation with the NSABP: the University of Pittsburgh, Maryland, Louisville, and Boston University.]

Each of the surgeons who participated in the Breast Project agreed to abide by specific criteria for the inclusion or exclusion of patients as outlined in a predefined protocol and to adhere to strict randomization procedures that divided the patients into treatment and control groups. Randomization was planned to prevent bias in selecting patients for a particular treatment. There were also plans for centralized data collection, evaluation, and review of pathologic material and a program for long range follow-up. The willingness among this group of surgeons to follow a predefined protocol represented the first such radical departure from conventional practice and set the stage for the more detailed and sophisticated protocols that were subsequently to be conducted by the NSABP.

Several years after the inception of the project, Drs. Irwin Bross and Nelson Slack assumed major responsibility for the biostatistical aspects and Dr. Robert Ausman for the general administration of the group. An executive committee of the investigators was formed early in 1964 to coordinate and direct the study and to provide more effective liaison among project participants. The first Executive Committee consisted of surgeons (Isidore Cohn, Jr., Louisiana State University; Edward Lewison, Johns Hopkins Hospital; Robert Radvin, University of Pennsylvania; and Louis Rousselot, St. Vincent's Hospital, New York) and radiation therapists (James Nickson, University of Chicago and Patrick Cavanaugh, Duke University). I was co-chairman of the group with George Moore.

In a letter to me on March 20, 1967, Dr. Noer indicated that he thought the upcoming grant renewal scheduled for the fall of that year would be an appropriate time for a change in the leadership of the project and suggested that I consider becoming a candidate for the chairman's position. I was appointed the new chairman of the Surgical Adjuvant Chemotherapy Breast Project on May 9, 1967. For the next three years, the operations and statistical centers of the group remained at Roswell Park, while I interacted with them from Pittsburgh.

Early Clinical Trials: The first Surgical Adjuvant Chemotherapy Breast Project trial, Phase 1 (a term that should not be confused with the current definition of Phase 1 trial) compared the outcome of patients treated by radical mastectomy with or without the administration of thiotepa. The study accrued 826 acceptable patients between April 1958 and October 1961 – a remarkable achievement for that time. The results of the Phase 1 study provided the first evidence that the use of chemotherapy could significantly decrease early recurrence rates in some patients and demonstrated, for the first time, that the outcome of patients with 1-3 positive nodes was different from that of patients with 4 or more positive nodes. However, because not all patients benefited from the chemotherapy, and because it did result in toxicity (although much less than is readily acceptable today), surgeons were reluctant to accept the use of systemic therapy.

When patient entry into the Phase I program was completed, a new study, Phase II, was initiated. Its objective was to evaluate the worth of 5 fluorouracil (5-FU), as compared with TSPA and to ascertain the value of postoperative radiotherapy and prophylactic oophorectomy. Findings from the Phase II trial demonstrated no advantage from the use of 5-FU over TSPA and showed that the toxicity resulting from the 5-FU regimen was, in fact, of greater magnitude.

In 1961, as part of the Phase II study, a randomized trial was begun to resolve the uncertainties that existed with regard to the worth of administering postoperative parasternal, axillary, and supraclavicular radiation therapy as an adjunct to radical mastectomy. The data, obtained through 5 years of follow up, failed to confirm conclusions derived from anecdotal information that had been derived using similar radiation techniques, which indicated an improvement in survival. Our findings resulted in great controversy. It is interesting to note that, 40 years later, uncertainty still exists with regard to the worth of using postoperative radiation therapy to improve survival outcome.

Because uncertainty also existed at that time with regard to the use of prophylactic oophorectomy as an adjunct to radical mastectomy, in 1961 we initiated a randomized clinical trial to evaluate that treatment regimen in premenopausal breast cancer patients. Preliminary findings through 3 years of follow up indicated no difference in either recurrence or survival data among patients who had been treated by either oophorectomy, TSPA, or placebo. Accruing patients to the study was difficult because there was a lack of appreciation

of the urgency for resolving that question – a situation that was to prevail for the next three decades. This study and the trial that evaluated postoperative radiation therapy were never updated because, after the group relocated to Pittsburgh, the data were never made available.

The Use of Clinical Trial Information to Generate Hypotheses: From the data collected in both the Phase I and Phase II studies, it became possible to relate patient outcome to information about the location of a breast tumor. At that time, it was widely believed that patients with tumors in the inner quadrants of the breast had a poorer prognosis than those with lesions in the outer quadrants. An evaluation of more than 1000 patients in our studies indicated that the location of a tumor was unrelated to prognosis and led me to conclude that there was no justification for selecting specific surgical or radiation approaches to treatment based upon tumor location.

Information from the patients entered into these trials demonstrated that, the larger the tumor, the more likely that axillary nodes would be positive, more nodes would be involved, and outcome would be poorer and led me to conclude that size was not necessarily related to “earliness” or “lateness” of a tumor and was not as consequential as other factors relative to the tumor and/or host that determine the development of metastases.

In the studies, recurrence and survival rates were correlated with number of lymph nodes examined in surgical specimens. Results indicated that the examination of a greater number of nodes in a specimen was no more meaningful in determining prognosis than examination of only a few. Those findings continue to have relevance to current arguments about the management of the axillae of patients with breast cancer.

The era between 1957 and 1969 was a learning period in the conduct of clinical trials, especially with regard to experimental design. In retrospect, the early trials of the Surgical Adjuvant Chemotherapy Breast Project were too complicated and represented a desire on the part of investigators to answer too many questions at once. This circumstance led to my view that clinical trials should be kept simple and that only a few questions should be answered in any single study. Although the overall results of those trials were viewed as disappointing, they were the first to demonstrate that cooperative studies using adjuvant therapy could be effectively

carried out among large groups of investigators nationwide.

Relocation: Soon after I was appointed chairman of the Breast Project, it became apparent that the situation I inherited was less than optimal. Dr. Moore's interests had shifted away from the project to his own research efforts, and, in addition, surgeons in the group had become disenchanted with the use of adjuvant chemotherapy. Moreover, there was a lack of unanimity among medical oncologists as to what new agents might be appropriate for testing in clinical trials. These specialists were not acknowledged as contributors to the early history of the project because medical oncology was just beginning to be identified as a specialty, and they were concerned primarily with the treatment of advanced breast cancer. As medical oncologists increased in number and became interested in the treatment of patients with earlier disease, they began to play a major role in the group.

During the next few years, the activities of the Breast Project were directed toward group cohesiveness, accumulating data in the ongoing trials, and gathering support for new protocols. Consideration was also given to the design of a trial to determine whether the Halsted radical mastectomy was more effective than breast-conserving procedures. Unfortunately, funding and other support from the NIH was at a low point; this contributed to a decrease in investigator interest. In addition, because advanced communications technology was still in its infancy, it became increasingly important for me to consider centralizing the operations and statistical components of the project in a single location. A fortuitous circumstance, which I will outline in my next installment, permitted centralizing all the activities of the Breast Project at the University of Pittsburgh in 1970.

The years between 1957 and 1969 not only gave rise to the use of the clinical trials mechanism for the evaluation of adjuvant therapy in the treatment of operable breast cancer, but also demonstrated how findings from such trials could provide information for augmenting existing biological hypotheses and generating new ones. This period was particularly significant from my perspective because it introduced me to clinical trials process and stimulated my interest in tumor metastases. During the late 1950s and 1960s, my laboratory associates and I published our findings in more than 50 scientific journals. The information from our studies led me to formulate an alternative hypothesis that became the basis for a new generation of NSABP clinical trials.