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BREAST CANCER, 1976

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KANSAS STATE UNIVERSITY



HEARING BEFORE THE SUBCOMMITTEE ON HEALTH OF THE COMMITTEE ON LABOR AND PUBLIC WELFARE UNITED STATES SENATE NINETY-FOURTH CONGRESS

SECOND SESSION

ON

EXAMINATION ON THE TREATMENT OF BREAST CANCER,
WHAT TREATMENT IS BEST, WHERE PHYSICIANS DIFFER,
AND THE RISKS AND COSTS INVOLVED

MAY 4, 1976



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(II)

CONTENTS

CHRONOLOGICAL LIST OF WITNESSES

TUESDAY, MAY 4, 1976

	Page
Kushner, Rose, author, Bethesda, Md.....	3
Rauscher, Frank J., Jr., Ph. D., Director, National Cancer Institute, National Institutes of Health; Vincent T. DeVita, M.D., director, Division of Cancer Treatment, National Institutes of Health; and Bernard Fisher, M.D., professor of surgery and director of oncology, University of Pittsburgh.....	17
Crile, George Jr., M.D., emeritus consultant, Department of General Surgery, Cleveland Clinic.....	38
Haagensen, Cushman D., M.D., emeritus professor of clinical surgery, College of Physicians and Surgeons, Columbia University, accompanied by Darrow Haagensen, M.D., Ph. D., Department of Surgery, Duke University; and Sven Kister, M.D., associate clinical professor of surgery, Columbia University.....	49

STATEMENTS

Columbia University College of Physicians and Surgeons, Cushman D. Haagensen, M.D., emeritus professor of clinical surgery, prepared statement.....	63
Crile, George Jr., M.D., emeritus consultant, Department of General Surgery, Cleveland Clinic.....	38
Prepared statement.....	45
Haagensen, Cushman D., M.D., emeritus professor of clinical surgery, College of Physicians and Surgeons, Columbia University, accompanied by Darrow Haagensen, M.D., Ph. D., Department of Surgery, Duke University; and Sven Kister, M.D., associate clinical professor of surgery, Columbia University.....	49
Prepared statement.....	63
Kushner, Rose, author, Bethesda, Md.....	3
Rauscher, Frank J., Jr., Ph. D., Director, National Cancer Institute, National Institutes of Health; Vincent T. DeVita, M.D., director, Division of Cancer Treatment, National Institutes of Health; and Bernard Fisher, M.D., professor of surgery and director of oncology, University of Pittsburgh.....	17

ADDITIONAL INFORMATION

Articles, publications, etc.:	
Breast cancer demonstration and education activities conducted by the National Cancer Institute.....	21
"Carcinoma of the Breast: Status of Adjuvant Medical Treatment", by Vincent T. DeVita, Jr., M.D., Director, Division of Cancer Treatment, National Cancer Institute National Institutes of Health, Bethesda, Md.....	68
Treatment options available to women from the National Cancer Institute.....	29
Communications to:	
Kennedy, Hon. Edward M., chairman, Subcommittee on Health, from Frank J. Rauscher, Jr., Ph. D., Director, National Cancer Program, National Institutes of Health, June 9, 1976.....	62
Rauscher, Frank J., Ph. D., Director, National Cancer Institute, National Institutes of Health, from Edward M. Kennedy, chairman, Subcommittee on Health, May 14, 1976.....	61

EXHIBIT 100-7-10-1

Page 1 of 1

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BREAST CANCER, 1976

TUESDAY, MAY 4, 1976

U.S. SENATE,
SUBCOMMITTEE ON HEALTH OF THE
COMMITTEE ON LABOR AND PUBLIC WELFARE,
Washington, D.C.

The subcommittee met at 9:35 a.m., in room 4232, Dirksen Senate Office Building, Senator Edward M. Kennedy (chairman of the subcommittee) presiding.

Present: Senators Kennedy and Schweiker.

Committee staff present: Philip Caper, M.D., professional staff member; and Jay B. Cutler, minority counsel.

Senator KENNEDY. The Subcommittee on Health will come to order.

The hearing this morning on the treatment of breast cancer is the first of a series of hearings that will occupy the Subcommittee on Health during the coming months. The hearings will be concerned with areas of medical care where it is unclear what treatment is best, where physicians differ widely, and where high risks and costs are involved for the patient and for our whole society. Our purpose is to determine whether we as a society are doing all we can to resolve the scientific disagreements with appropriate medical research, to assure that physicians are aware of the latest medical advances, and to protect the patient's rights of choice when so much is at stake and where so little is certain.

The American public invests billions of dollars in medical research and development. We have created the most powerful basic research capacity in the world. We must work to maintain this capacity. Ultimately new knowledge is our best hope against much human disease—and an essential foundation for providing good health care to the American people.

But to provide good health care, we must convert our latest knowledge into proven treatments—and we must assure that these treatments are understood and used properly in hospitals, clinics, and doctors' offices across the country.

There is growing interest in medicine in clinical trials as a means for determining whether new treatments are effective. We intend during our hearings to review the potential of clinical trials. We intend also to examine the extent to which we can strengthen our efforts to assess the importance of new technologies and to convert the promising results of biomedical research into better quality health care for all Americans. On June 16 and 17, the subcommittee will hold hearings on "Basic Issues in Biomedical Research" when these and other areas which will become the basis for hearings on biomedical research over the course of the next year will be explored.

It is very appropriate that the first of these hearings be devoted to the treatment of breast cancer. This disease is one of the leading causes of death among women within the United States. Seven percent of all women will contract breast cancer at some point during their lives, 90,000 new cases of breast cancer are reported each year, resulting in over 32,000 deaths.

Moreover, after years of research and experimentation, there is no certain cure for the disease; in fact, wide variation exists among knowledgeable physicians with respect to the best treatment for this disease. Some experts believe that radical mastectomy is the therapy of choice, while others argue that a simpler and less disfiguring surgical procedure may be just as effective. A recent study by the National Institutes of Health (NIH) calls into question the necessity for some of the radical breast cancer operations which have been common medical practice in the past. If this study is correct, then many women may be saved from unnecessary physical and psychological scarring and disfigurement in the future.

This disagreement is of deep significance for the public. No patient wishes to face more extensive surgery than is necessary, and certainly no physician wishes to perform it without maximum assurance that it is the best way to save life, and to diminish suffering.

In the face of these disagreements, and of the importance of surgery to the patient, valid questions must be raised with respect to the patient's right to share in the decision concerning the type of operation to have. Here, the question of one step versus two-step mastectomy enters, and the question of the role of the patient in choosing the therapeutic modality to which she will be subjected is raised. Is it proper and necessary that a woman suspected of having breast cancer be put under anesthesia for a surgical biopsy or exploratory operation and awoken to find that a radical mastectomy has been performed?

Because of these and other questions, the committee will hear this morning from a number of specialists in the treatment of breast cancer as well as from consumers active in promoting awareness with respect to the consequences of breast cancer and its therapy. The committee believes that this controversy concerning the appropriate treatment of breast cancer, which has racked the medical profession over recent years, should be debated in a public forum. Despite the great sophistication of much of the medical care delivered in this country today, honest disagreements exist not only with respect to breast cancer, but also to the appropriateness of clinical procedures for a number of different diseases.

We hope that the expert witnesses at these and subsequent hearings will not only help us to formulate more clearly these and other pertinent questions, but may help point the way to a solution to some of these important problems, which are of such great importance not only to the medical profession, but to the public at large.

Mr. Schweiker.

Senator SCHWEIKER. Thank you very much, Mr. Chairman.

I want to commend you for holding these hearings.

I think they are very significant in two respects. First, the questions surrounding the necessity of some of the techniques that we are using surgically on breast cancer patients today are very significant and need to be aired and discussed.

But second, I think we are coming to a time when the investment that this country has made in research, particularly in cancer research, is just beginning to pay off.

We are seeing new and significant technological breakthroughs in cancer, not just in breast, but in others as well. And second, we probably have had more money available for cancer than for any other disease in the history of the world. And I think the question that we have to ask is how to join the two, the new technology and the money, so we invest it wisely and utilize the resources that have now become available with the technologies to solve as many of the terminal cases and eliminate as much of this hardship disease as possible.

Perhaps it is good news we have to face this decision, because up til recently, we have not had those options. But since we do have the options, I think it is important to hold these hearings and I am glad to participate.

Senator KENNEDY. I am glad Senator Schweiker mentioned the issue of clinical research, because that is something we are going to look at closely. The President's panel that will be reporting to us on the NIH, making recommendations to us and doing evaluation on basic and clinical research. I think all of us recognize the preeminence of the NIH basic research areas and are strongly committed to its excellence and continuation, but we also want to make sure some of the benefits of that particular research are getting out to the people. The kind of priority that clinical research has is very important.

These are important clinical research ethical issues that we are going to discuss this morning. For example, what happens when a doctor knows a particular treatment is better and yet recommends to the patient that she be involved in a clinical trial. What are the ethical issues? What should the patient know? How should they be informed? And what choices should be made available to her?

There are some extremely important and very, very significant issues that I think can have enormous importance to the well being and the health and the safety of the American citizen, in this case the American woman.

So we will look forward to this hearing this morning. We will start off with Mrs. Rose Kushner, who is the author of a best selling book entitled "Breast Cancer: Personal History and an Investigative Report."

I welcome her this morning.

STATEMENT OF ROSE KUSHNER, AUTHOR, BETHESDA, MD.

Mrs. KUSHNER. Thank you, Senator Kennedy and Senator Schweiker.

My name is Rose Kushner, and I am a medical writer.

In June of 1974, I found a symptom of breast cancer. Because I live near the National Institutes of Health and the National Library of Medicine, and because I can understand medical language, I had access to the vast amount of literature about the current status of breast-cancer treatment. I also had friends in the medical profession to advise and help me to obtain the safest and least disfiguring treatment, according to opinions prevalent 2 years ago.

Most women are not as lucky as I was. They have neither the background nor the advice I had, and they must blindly follow whatever procedure their physicians recommend. In this country, this procedure is being wheeled into an operating room, being put to sleep and having the suspicious area cut out. The specimen is immediately sent to a pathologist—while the woman remains unconscious on the table—and the tissue is examined by microscope.

If it contains only benign, or nonmalignant cells, word is sent to the surgeon right away. The incision is closed, and the woman can go home to celebrate her verdict within a day or so. However, if the specimen contains invasive cancer cells, surgeons in the United States usually proceed to perform a Halsted radical mastectomy. This is an extensive operation in which a woman's entire breast is amputated. In addition, her pectoral or chest muscles—all she has separating her skin from her bones—and as many lymph nodes or glands in that armpit as possible, are removed at the same time.

Therefore, in the United States, most of the 90,000 women who are expected to discover breast cancer in 1976 will be put to sleep without their knowing whether they will wake up with one breast or with two. And, most of the time, the amputation will be the Halsted radical mastectomy which leaves ugly scars extending into their armpits, and dips and hollows in their chests. Of course, the degree of disfigurement varies with the skill of the surgeon.

In addition to scars, dips, and hollows, the Halsted radical and its deep cutting into the armpit to remove hard-to-reach lymph nodes, frequently causes lymphedema—unattractive and sometimes painful swelling of the affected arm.

Trapped lymph fluid going into the arm is blocked from returning to the body, and the result is often so much swelling that circulation of the blood is impaired. In the most extreme cases, the arm must be amputated to prevent gangrene.

So much mutilation and pain—physical and psychological—would be entirely justified and worthwhile if they were imperative to save or prolong life. But this is not the case. Scientists all over the world have shown that survival rates are the same after the venerable Halsted radical as are the survival rates after the less-extensive modified radical mastectomy, the operation performed on me.

Prior to this surgery, I did have a diagnostic biopsy, but it was done as a separate procedure. I had learned that amputating the breast immediately after the quick pathological examination—the frozen section—is not medically necessary. Instead, I discovered, many authorities here and abroad consider it physically beneficial to wait between the two procedures to do vital tests that may tell them if the cancer has spread to other organs. Certainly, from the psychological point of view, every woman understands the benefit of having a few days or a week to get another opinion or another surgeon, to arrange for household help, a replacement at work and—above all—to have time to shift her emotional gears and adjust to the knowledge that she must lose her breast.

I also learned that removing the chest muscles and the lymph nodes high in the armpit does not influence survival rates in spite of the arguments that the pectoral muscles may be harboring cancer. True,

more women are living longer after breast surgery today than were surviving at the turn of the century when the Halsted was introduced. But the lengthened survival rates are the result of improved surgical techniques, antibiotics and post-operative care—not of the operation itself.

Knowing this information helped me decide what to do in my own situation. After my mastectomy, I wanted to share this knowledge with women who are not lucky enough to be able to use medical libraries. To do this, I wrote a book—"Breast Cancer: A Personal History and an Investigative Report"—which was published last September. By translating information from medicalese into plain English and aiming it directly at women—the ultimate consumers of these medical services—I hope I will help break the old-fashioned habit surgeons in the United States have followed for the past 75 years.

From what I have read about Dr. William Stewart Halsted, I am sure that if he were alive today, he would be the first person to put the mastectomy that bears his name on a museum shelf next to the leach.

But abandoning the Halsted radical mastectomy is not enough. While the modified-radical preserved my muscles and left my neckline and arm free of scares and swelling, my breast and many of the lymph nodes in my armpit were cut out.

Was this operation really necessary?

I do not know; no one knows.

I decided on this operation because the authorities I consulted told me that—as far as current data are concerned—the modified-radical is the safest and least disfiguring surgery. That is, as far as anybody knows now or knew back then.

There is a multitude of lesser surgical procedures advocated by highly respected physicians here and in other countries. There is such a multitude, as a matter of fact, that women are thoroughly confused by the constant stream of announcements that always follow medical and surgical meetings.

There is the lumpectomy, tylectomy or local excision: removal of only the malignant tumor. Another is variously known as wide excision, wedge resection, segmental resection or partial mastectomy. Sometimes, these surgical procedures are accompanied by the removal of many lymph nodes; sometimes, only one or two are cut out. Often these lesser procedures are followed by miscellaneous types of X-ray treatment. There has recently been talk about substituting some kind of drug treatment—chemotherapy—for the radiation.

In all these operations, more than the tumor is removed, but the breast remains. Depending on its original size and the size of the tumor, the breast may look the same or be smaller. But it is still a breast.

Still another operation is the simple or total mastectomy, an operation in which the breast is removed, but the lymph nodes and chest muscles are preserved. Again, this surgery may or may not be followed by X-ray in certain cases.

All these procedures are as highly respected in many countries of the world as the Halsted radical mastectomy is in the United States. And all of these procedures have staunch advocates in our country. But none has gained the support of the majority of U.S. surgeons, because none is considered to be "as good as the Halsted"—the U.S. measuring

stick. Not that the Halsted has such impressive survival rates. The women who have this mastectomy have an overall 10-year survival rate of only 50 percent.

However, as far as anyone knows now—or knew in 1974 when I studied the statistics—nothing is any better.

So even now, in 1976, all breast-cancer surgery is compared to this antique yardstick: the modified is “as good as”; lesser procedures are “not as good as.” But no one really knows with any certainty, because, I have been told, there have been no controlled clinical trials of surgeries less extensive than mastectomies of some kind.

Senator KENNEDY. You would recommend such trials, would you?

Mrs. KUSHNER. I do not think you would get many people to cooperate, and I will explain this in the rest of my testimony.

In plain English, a “controlled clinical trial” is a comparison between different treatments, a comparison scientifically ruled by certain limits and restraints. First, the patients are matched as much as possible for age, phase of disease and so on. Then patient No. 1 receives treatment A, patient No. 2 receives treatment B and 3. C. Until such controlled trials are held and the women are followed for 5 or 10 years, so their recurrence and survival rates can be evaluated, I have been told, the National Cancer Institute has no alternative but to advocate some kind of amputation of the breast as the safest and least disfiguring surgical treatment available.

But to women, losing their breasts is in itself disfigurement. Hardly a week goes by without an article in a newspaper or magazine describing this or that procedure. Magazine articles and even some books have been written by women who opted to have lumpectomies, women who are doing very well without losing any part of their breasts except the cancerous tumor.

Since 1 of every 15 U.S. women will develop cancer of the breast some time in her life, these articles and books are avidly devoured. Every time a woman broadcasts a “success story” of her victory over cancer without mastectomy, those of us who obeyed the dictates of the data wonder if we lost our breasts for nothing.

So what is a woman to do? Few of us would risk death because of vanity or body-image or symmetry. And yet—does the breast really have to be amputated to give us the best chance for living?

Because my book has made me someone to turn to for information, I have by now assisted more than 3,000 women through a breast cancer advisory center which was begun for this purpose. The most frequent and poignant question asked is, “Is there not any alternative to losing my breast?” Based on the results available today, I can only answer that there is not, unless the woman wants to gamble with her life.

Will there ever be any alternative? We women look to the National Cancer Institute to give us the answer, once and for all. If controlled clinical trials are essential, why have they not been done?

There appear to be at least two major obstacles.

Surgeons I have interviewed about participating in clinical trials say they cannot, in good conscience, give a woman treatment A simply because she is patient No. 1 and treatment B to the next woman, just because she is patient No. 2. They feel that many factors must be taken into account before deciding on how much to cut and what to keep. For example, the woman’s age, other physical problems and the

degree of invasiveness of her particular kind of cancer, I have been told, should help determine the kind of surgery used.

Senator KENNEDY. Do you think the physician or surgeon has the data and information necessary to make that kind of decision?

Mrs. KUSHNER. He should, or else he should turn in his license.

Senator KENNEDY. Well, do they?

Mrs. KUSHNER. Well, the pathologist—if he or she does the frozen section, which is done within minutes, would reveal to the surgeon whether the lesion is malignant or benign. But the very careful pathological studies the “permanent section”—and you could get more information from Dr. Fisher later—would be able to reveal to the surgeon the kind of cancer it is and other factors. There are many different kinds of breast cancer with varying degrees of invasiveness. Pathologists count the mitotic activity to see how many cells—

Senator KENNEDY. I was thinking on this other point, age, physical problems, et cetera.

Mrs. KUSHNER. They know that if a woman is 65, there is no point in cutting her up to keep her alive for 30 years, you know. I think they usually know the woman's age. At least I hope so.

On the surface, this argument may seem like evasion, but—as a cancer patient—I understand it completely. I would not want to be randomized into treatment A or B, if A has 40 years of results based on tens of thousands of women, and B has 8 years of data from 90 patients. I would want treatment A. This is precisely the situation I faced in June 1974. I knew of the lesser procedures done in other countries and in various institutions by highly qualified surgeons here. All have advocates that say these are as good as the Halsted radical mastectomy so far. But that so far was not far enough for me to gamble my life on. And it still is not.

There must be some way out of this never-ending circle of question marks and doubts. From the point of view of a breast-cancer patient, it is difficult to believe that only total and absolute randomization of treatment and patients can finally reveal the data needed by surgeons. Why cannot volunteers be used?

Senator KENNEDY. Would you participate in a trial for surgery?

Mrs. KUSHNER. For surgery? No; if the situation should arise that I should need chemotherapy, I would, however.

Senator KENNEDY. I was thinking of the trial.

Mrs. KUSHNER. Not the surgical trial, no.

Senator KENNEDY. How are you going to get that clinical trial?

Mrs. KUSHNER. Well, I think there are enough volunteers and that we have enough computerization and technology that they ought to be able to figure out a way to use the people who are willing to volunteer on both sides—surgeons and women.

Senator KENNEDY. Well, you indicated, from your testimony, that you were fortunate in having a very broad awareness and understanding of the whole medical area and friends that could counsel you, and that you yourself would be extremely reluctant to involve yourself in clinical trials.

Mrs. KUSHNER. Of the surgery. With what is known now, yes.

Senator KENNEDY. Well, how do you expect to get any consumer really involved in any such clinical trial?

Mrs. KUSHNER. That is what I said to you earlier, I do not.

Senator KENNEDY. Then how are we going to resolve the issue?

Mrs. KUSHNER. I do not know, but that is not my problem. That is the problem of the National Cancer Institute. I am only a patient.

Senator KENNEDY. I know it is not yours. I am trying to get you to help us.

Mrs. KUSHNER. I am trying to.

Senator KENNEDY. Do you think it is possible?

Mrs. KUSHNER. Well, as I planned to say later but I will say it now, if computers can predict the results of a Presidential election on the basis of 5 percent of the votes before the polls are closed in California, I do not see why computers cannot predict the outcome of lesser surgical procedures for breast cancer without having vast, random, controlled clinical trials.

Senator KENNEDY. Well, they predicted Dewey over Truman and Udall over Carter in Wisconsin.

[Laughter.]

Mrs. KUSHNER. But overall, polls are usually better than that. And maybe they will get even better.

I just do not think relying on or ever having clinical trials with randomization is realistic, with informed consent in effect.

Senator KENNEDY. We have a number of women in the audience. How many of you would, if faced with this kind of problem, commit yourself to being involved in a clinical trial on this?

Mrs. KUSHNER. The important thing to remember is that one has many, many years and many, many patients of evidence and one is relatively new and has relatively few women. That is the balancing thing. If you do not know much about either one, you do not have much choice.

Senator KENNEDY. Fine, let us continue.

Mrs. KUSHNER. I ended with asking why volunteers cannot be used? I think that this question is worth repeating.

Why cannot volunteers be used? Why can not a controlled clinical trial be constructed utilizing those physicians and patients who are not only willing, but actually eager, to participate. I could list at least a dozen such physicians, and the breast cancer advisory center has heard from hundreds of such patients. Why can they not be brought together to test the various procedures in a scientific way?

When I ask this question, I am told repeatedly that "self-selection distorts the data." I am not a statistician and can neither argue against nor understand this statement. But on the other hand, I have never gotten an explanation to account for the distortion that "self-selection," by either the physician or the patient, causes.

But if this is considered to be a problem by the experts at the National Cancer Institute, can it not be solved by the sophisticated technology and expertise available today?

From the point of view of a breast-cancer patient, it is incredible that the outcome of a presidential election can be predicted on the basis of 5 percent of the vote, hours before the polls close in California—but comparing two kinds of surgeries needs special techniques.

From the point of view of a breast-cancer patient, it is impossible to understand why scientists who have computers that can send men to the moon, and bring them back, cannot make the adjustments and manipulations to correct for self-selection. Too many computerized miracles have taken place to have us believe that the only solution is random selection.

The second obstacle—and, I would like to insist a very important obstacle, that we women encounter is that the average general physician in the United States—the doctor treating most patients—pays little or no attention to the results of controlled clinical trials, even after they are done and published. Indeed, even the comprehensive cancer centers supported by the NCI—the National Cancer Institute—are not required to apply the results of such trials to the treatment of patients.

Senator KENNEDY. I think this is a terribly important point.

Mrs. KUSHNER. I do too.

Senator KENNEDY. You have been very helpful in identifying the problems that we are facing. I do not know whether you have any suggestions that could be made in this area.

I suppose we should ask what to expect, both from the Cancer Institute in terms of overseeing treatment, and from other agencies as well that are seeking new techniques in order to give assurance to people.

Mrs. KUSHNER. Well, from what I understand of the history of the National Institutes of Health—the law that permitted them to be created way back in the thirties—when the American Medical Association was much more powerful than it is today—placed two restrictions on the Government. One was that no one would be treated in any of the Institutes without a referral from a private practitioner, and the second one was that the NIH report only results of its research.

The Institutes are not permitted to make recommendations for individual treatment, legally.

It is done on a person-to-person level. I know, because I have been the beneficiary. But, according to official policy—and this was enunciated on September 30, 1974, very clearly, again and again and again, by both Dr. Fisher, who is here, and Dr. Nathaniel Berlin, who was at that time the chairman of the breast cancer task force—that they may not give recommendations for treatment. They may report only results of its research.

As far as I know, this restriction is still in effect. And I would say that it should be rescinded or repealed, or whatever has to be done legally to get it out of the way.

Second, in Canada—which is a free country—Alberta and Saskatchewan have passed laws forbidding any general surgeon from laying a knife to the skin of any patient without thorough study by an oncological review board.

When I was in the Soviet Union, I was told this is the law. When I was in England, it is voluntary. Even some Harley Street doctors will not fool with a breast-cancer patient. If a woman comes in with a symptom, she is either sent down to the Royal Marsden Hospital or to Guy's Hospital, which are the two cancer centers for London.

I mention that little England—bankrupt little England—is going to have 14 Government-supported cancer centers. These are not for Great Britain and not for the United Kingdom. Fourteen centers just for England. And the United States is only going to have 17.

Senator KENNEDY. In our last bill we authorized 40. But your point is well taken.

Mrs. KUSHNER. I know that the Senate, that this very committee recommended to the Senate, and the Senate passed a bill to ban diethylstilbestrol from livestock feed last year. But the bill is still locked up in the House. And I know that on January 21 of this year, Dr. Alexander Schmidt testified before this subcommittee that there is a link between breast cancer and oral contraceptives. But as of last Thursday, nothing was done in terms of warning women. So senatorial authorization of funds does not mean 40 centers will be built.

Senator KENNEDY. We passed a measure in the Senate but we still have not been able to get it.

Mrs. KUSHNER. Yes.

Senator KENNEDY. We passed it twice actually.

Mrs. KUSHNER. I know. Sad, isn't it?

Senator KENNEDY. It is sad.

Mrs. KUSHNER. Canada will not buy our beef because of that.

Senator KENNEDY. Twenty-six different countries will not buy it.

Mrs. KUSHNER. I wrote a letter to Mrs. Joan Braden about it, but she says it is not in her department. I do not know whose department it is in, but something should be done.

To get back to the average general physician paying little attention to NIH results and why. Then I talked about the law.

According to the laws governing the National Institutes of Health, only the results of research may be reported by this Federal agency; none of the Institutes may make recommendations for specific therapy. Certainly, having the Government demand that certain medical procedures be carried out or omitted is blasphemous in this country.

One example, in the case of breast cancer, are the controlled clinical trials of postoperative X-rays or cobalt treatments. Almost a decade ago, the NCI's experts conducted and announced data that proved definitely that such treatment does not increase survival rates at all. As a matter of fact, some studies suggested the radiation actually decreased women's lifespans by triggering other cancers. But, in spite of these published data, routine prophylactic X-ray treatment after radical mastectomy are still being given to American women by physicians all over this country.

Controlled trials of chemotherapy have shown that these highly toxic drugs must be administered by highly trained personnel, especially if they are given in combination. Yet, anticancer drugs like cyclophosphamide, 5-fluorouracil and methotrexate are being used everywhere by ordinary general practitioners, according to my neighborhood pharmacist.

As a matter of fact, I understand it is against the law for anyone but a trained chemotherapist to give combined chemotherapy and Dr. DeVita can corroborate me on that—but it is still being done.

There are, unfortunately, other such examples of either ignorance of or ignoring of the published results of controlled clinical trials. So,

insisting that random scientific comparisons must be done before anything else is known is an excuse that will not play in Peoria—or anywhere else. We women are bewildered and tormented by a welter of conflicting opinions, and we look to our tax-supported experts to tell us what to do.

A cure for breast cancer is, admittedly, too much to ask for from a computer. But a solution to a statistical problem should certainly be possible. I hope this Senate hearing is an indication that attention is finally being paid to this vital women's issue.

For the vast majority of us, staying alive has the highest priority, and physicians are certainly right when they tell us the loss of a breast is unimportant when life is at stake. But we live in a mammary-oriented culture where two—preferably large and shapely—breasts are essential for a woman's self-image. The women's liberation movement will not change this situation in the foreseeable future, and tens of thousands of women will continue to suffer from it.

Mastectomized women often refuse to shop for clothing, because they are unwilling to be seen by a saleswoman. I have been called by a man whose wife slashed her wrists during a depression when she returned home after surgery; young unmarried women are risking their lives—as far as anyone knows—by having lumpectomies, because they fear they will not get a boyfriend more than they fear cancer; older women believe—rightly or wrongly—that their mastectomies will drive their husbands to a “whole” woman because the loss of a breast has made them “part” woman.

This psychological and psychiatric anguish that frequently accompanies breast cancer has only recently been acknowledged by physicians as a medical problem that needs to be treated. It does little good to tell these women that they had to lose their breasts because their lives were at stake and they would have died otherwise.

Some would rather be dead.

To paraphrase what may be the most infamous quote to come out of the war in Vietnam, a mastectomy—too often—destroys a woman's life in order to save it.

Senator KENNEDY. Thank you very much—very powerful testimony and comment on a problem which obviously is of enormous importance to our country and to the women of the Nation.

We will hear during the course of our hearing this morning a strong advocate in favor of radical mastectomy and we will hear strong criticism in opposition to it.

Not being trained as medical practitioners or doctors, the most any of us can do is to legislate or allocate resources, and try and develop procedures in which the truth will emerge. Perhaps the best way of treating any such circumstances will emerge, and then we can legislatively deal with those particular issues.

But obviously we cannot treat patients—and no one should expect that we would be able to.

In trying to pursue the best method of treatment, it seems to me that one of the ways, perhaps not the only way, is in the area of clinical trials.

And you mentioned, I think people would be reluctant to involve themselves in clinical trials. And I think others just in the audience listening to your testimony, and perhaps even prior to coming here, would have the same point of view. What you suggest is that we review the existing documentation, the existing figures, the existing studies and try to correlate them in such a way as to be able to expect the Cancer Institute to draw up some firm conclusions on it. And we will certainly ask Dr. Rauscher and the Cancer Institute if they can do it; if not, why not?

But I want to understand completely any recommendations that you do have and the ways we can best proceed. I think the kinds of problems you faced will be faced by hundreds—tens of thousands of women, and, after having read of these hearings or your book or other reports, are going to wonder what is the best step to take?

Mrs. KUSHNER. Last July 1975, Dr. Vera Peters of the Princess Margaret Hospital in Toronto, published a report which was not available when I had to make my decision in June 1974. She has 30 years worth of data comparing a Halsted radical mastectomy plus post-operative radiation, with wide excision plus radiation of the breast. I guess she had 200-some-odd women in each group. The wide excision plus the radiation lived longer in the 30-year followup.

Dr. Eleanor Montague at the M. D. Anderson Hospital in Texas, Dr. Samuel Hellman and Dr. Eric Weber at Harvard in Boston, Dr. Leonard Prosnitz at Yale, New Haven—there are highly qualified and very well respected surgeons all over the country who feel strongly that it is unnecessary to take off a woman's breast to treat cancer. And they are getting people to come to them.

They use various kinds of radiation, they use radioactive implants—and there are women who are willing to do this, in fact—eager to do this. I simply do not understand this self-selection business that prevents them from being used for study.

Senator KENNEDY. Do you think we should legislate a prohibition for radical mastectomy?

Mrs. KUSHNER. No; I do not think so. It is a free country. But I do think women should be made aware that—that is why I wrote the book—other options exist. I think women should be made aware a Halsted radical—is not necessarily the best and usually no better than the modified. I had the modified, but if I had a Halsted, I would not be wearing this neckline. I would have to hide my upper chest.

However, I do not see how you can legislate a surgical procedure and still consider this a free country.

I do think you can get rid of the restriction on NIH. I think the—

Senator KENNEDY. Do you think there should be a much greater responsibility? You think, as I understand, that is the responsibility by the Cancer Institute to educate every surgeon in this country dealing with this.

Mrs. KUSHNER. I certainly do, but I do not know if it is legal. I certainly would like to see physicians required to be recertified periodically. People who deal with cancer surely need continuing recertification, because there are so many advances. So many physicians graduated from medical school, or finished their residencies years ago that unless they have continued learning—most of the surgeons are

"he's"—unless they have kept up with what is going on, they have no more business treating cancer than you or I.

Senator KENNEDY. And an important point.

That is why I think we have some real responsibilities for continuing education programs for all those in the health professions areas. That is something that we have been trying to deal with in the medical profession.

Mrs. KUSHNER. Is it possible to pass the kind of law that Alberta and Saskatchewan have passed so that no surgeon may operate on a cancer patient without having the case studied by a cancer review board? Is that legal? I do not know the legalities involved or what the law is.

Senator KENNEDY. You possibly could do it with regard to Federal—

Mrs. KUSHNER. I cannot understand why the National Cancer Institute in its own cancer centers—does not say, "This is our policy; you have got to do this." I have written to the breast-cancer departments of the different NCI cancer centers, and have discovered they are very autonomous. They do not have to follow the policies of the NCI at all. If they want to, that is fine. But if they do not, they do not. I do not understand how this can be allowed.

Senator KENNEDY. We are going to hear from the Cancer Institute on this particular point.

Senator Schweiker.

Senator SCHWEIKER. Thank you, Mr. Chairman.

First I want to compliment you, Mrs. Kushner, for so eloquently summarizing the dilemma that we have before us—this issue and other issues.

The question I had—and you mentioned in your testimony that because you have done some preliminary work and become knowledgeable about what was going to happen to you, you asked to have a separate diagnostic biopsy first and that this option is usually not given to women today.

I just wondered if you had any figures or any indication of exactly how this procedure works?

Mrs. KUSHNER. I know that until my book came out in September 1975, it was very difficult to do. I asked the surgeon to sign a contract forbidding removal of my breast under any circumstances, and 19 surgeons turned me down.

Senator SCHWEIKER. Nineteen surgeons turned you down?

Mrs. KUSHNER. My mammogram, my breast X-ray was benign. It was a "false negative." The 20th surgeon I called thought I was just being a ridiculous "women's libber," and he signed the contract. He was rather angry with me afterward. That contract is printed in my book.

Before my book was published, as far as I know, the two procedures were usually separated if the frozen section was equivocal and the pathologist could not tell whether it was malignant on immediate inspection. Then surgeons would close the woman up and have her come back later, if necessary. This, indeed, was what motivated me to investigate further. If it is safe to wait for these women, why is it not safe to wait for all women?

Senator SCHWEIKER. Let me understand that again. Nineteen surgeons turned you down—in what request specifically?

Mrs. KUSHNER. To separate the two procedures; to do a biopsy, close me up and diagnose the specimen by a careful permanent section. Then, if I had cancer, to let me shop for a specialist to do the mastectomy.

Senator SCHWEIKER. What was the rationale of the doctors who turned you down?

Mrs. KUSHNER. Some laughed at me. Some hung up on me. Some said, "No patient is going to tell me what to do."

Senator SCHWEIKER. And I gather this is still par for the course?

Mrs. KUSHNER. Fortunately, it is changing, I understand. Dr. R. Robinson Baker, chief of breast surgery at the Johns Hopkins Hospital, told me they are doing 90 percent of their biopsies under local anesthesia, in the emergency room or in the outpatient clinic, without putting the woman to sleep at all, as a separate procedure.

Senator SCHWEIKER. And you have—

Mrs. KUSHNER. It is a habit that got started, I think, because when hospitalization insurance plans first got started, they paid for no surgical procedure that was not done in a hospital operating room. It just persisted.

At one time, there was a real fear that the cancer would spread, but this has been known to be untrue for over 25 years.

Senator SCHWEIKER. What would you guess? I guess this is only an estimate; how many might turn you down today? In other words would that figure—

Mrs. KUSHNER. I do not think anybody would turn me down today. [Laughter.]

Senator SCHWEIKER. I realize you are a special case. But suppose your name was not Mrs. Kushner?

Mrs. KUSHNER. Most surgeons still refuse.

Senator SCHWEIKER. How many would turn you down today?

Mrs. KUSHNER. Most women still have a hard time, I know, because they call me through the Breast Cancer Advisory Center for names of surgeons who will.

Of course, if the mammogram, other tests, and the surgeon's examination all indicate that it is cancer—there are some ways to know for sure in advance—then there is no reason for a separation. "Staging" tests—bone scans, chest X-rays, liver studies, all the things to make sure that it is not elsewhere—are done ahead of time, and the woman is prepared emotionally to wake up with one breast gone. Otherwise, "staging" is done afterward.

It is estimated that 50 percent of all women have microscopic cancers somewhere in their bodies, in other organs, at the time of mastectomy. This number is based on the knowledge that, during the first 5 years, about 50 percent of the cancers will recur.

But we only have the technology to find about 13 percent of these micrometastases by scans, X-rays, and so on. They cannot all be found. But these tests should be done, before a breast is amputated.

There is no point in removing a woman's breast if cancer is already in her lungs, bones, or liver, unless it is an ulcerated kind of cancer. In that case, a surgeon would just do a simple mastectomy to prevent

infection or other complications. But there is no point in taking out the woman's muscles and nodes if disease is already in a distant organ.

The reason for doing a mastectomy at all is to keep the cancer from spreading to another organ. If it has already spread, why do it? Many breasts are cut off for nothing because the surgeon does not stage to look for cancer elsewhere in advance.

Senator SCHWEIKER. What factor enters into this decision process?

Suppose you had a reasonable expectation—I am just creating a hypothetical case—that your chemical cures might well work, where would you work to go get a decision? Would the surgeon make a decision as to the use of chemical cures as opposed to surgery?

Is there a factor here that a surgeon decides the issue because he is a surgeon?

Mr. KUSHNER. Surgeons do decide far more than they are capable of deciding. [Laughter.]

Most general surgeons do not have any expertise in treating cancer. There are encological surgeons—cancer surgeons—but most general surgeons should take out the stitches, see that the wound is healed and send all cancer patients to cancer specialists. The average general surgeon has no business treating cancer unless he has had special training. But most do, yes. Unfortunately.

As far as I know, nobody is advocating chemotherapy without preliminary surgery. In the case of breast cancer, a surgeon has to at least take out the lesion to know if it is cancer in the first place. So there must be some surgery.

Senator SCHWEIKER. When you have got a cancer specialist today—

Mrs. KUSHNER. Yes.

Senator SCHWEIKER [continuing]. Is he normally a surgeon now or not for breast cancer? Or not necessarily—

Mrs. KUSHNER. Most women go to their gynecologists, physicians who are absolutely the wrong people to go to for breast problems.

Senator SCHWEIKER. Then they get referred?

Mrs. KUSHNER. To a surgeon.

Senator SCHWEIKER. To a surgeon.

Mrs. KUSHNER. If he is a good guy, he will take out the stitches—and I say "guy" advisedly because, as I said earlier, surgeons are almost all men in the United States.

Senator SCHWEIKER. What I am getting at is if a surgeon makes a decision between surgery versus chemical therapy—

Mrs. KUSHNER. Some surgeons give chemical therapy.

Senator SCHWEIKER. I understand that and some do not, and the question is, is that really an objective way to go?

Mrs. KUSHNER. It depends on his training. The American Society of Clinical Oncology is only 4 or 5 years old. There is still no College of Surgical Oncology.

I do not know why. Perhaps Dr. Fisher could tell us about it. There are many men who are technically general surgeons, but, because they have devoted a great deal of their careers to cancer surgery, they are oncological surgeons, even though there is no official society

or board. So all general surgeons who treat cancer cannot be condemned. But most should only do the cutting. The American College of Surgery conducted an informal poll at its last convention and found that the average general surgeon does only about 10 mastectomies a year. I know of doctors who do more than that in 1 month. So the criterion should be their training and experience rather than the professional tag they wear.

Senator SCHWEIKER. It gets back to whether you ought to have your tonsils out or adenoids out; who makes that decision? Usually the surgeon.

We went through a whole spell there where everybody was taking all those things out, and then all of a sudden we decided maybe that was not such a good idea after all.

Mrs. KUSHNER. At least it was an ear, eye, and throat specialist, not the kind that takes out appendices, hernias, and gall bladders. Usually you have a man who at 8 o'clock in the morning does an appendectomy; at 10 o'clock, an ulcer; then he may grab a sandwich and do a gall bladder at 2; 4 o'clock he takes out somebody's prostate. Once in a while he does a mastectomy.

At least tonsils are done by people who have some special training—otorhinolaryngologists I think they are called.

I do not know any general surgeons, except in small towns where there is only one person who knows how to use a knife at all, where general surgeons do tonsilectomies. But every surgeon feels competent to do a mastectomy. I do not think every surgeon is.

Senator KENNEDY. Could I ask you, is there a difference in the reimbursements to surgeons under a general insurance program for radical mastectomy and—

Mrs. KUSHNER. Yes.

Senator KENNEDY. Would you tell us about that?

Mrs. KUSHNER. There is a system called the California Relative Value Scale is a point system for payment or fee schedules.

Senator KENNEDY. What is a point system?

Mrs. KUSHNER. The California Relative Value Scale is a mechanism devised by insurance companies. Depending on the part of the country—when I did the research on this, Manhattan was the highest and Montana was the lowest—each kind of surgery is assigned a certain point value. Each point has a specific dollar value for that geographical location. When I checked, a Halsted radical mastectomy was worth something like 55 or 60 points and modified mastectomy was worth 30 points, and I guess a lumpectomy would be worth 5. Depending on what each point is worth in dollars in that geographical area, that is the way the fee the doctor is paid is calculated.

My biopsy was done in a hospital, because I did not know any better then. The surgeon got \$200 for the biopsy—for just removing the lump—and he got \$30 for the two office visits. So that was \$230 just for him.

Then, I paid for a room, I paid for the operating room, I paid for the recovery room, I paid for the anesthesiologist. That 20-minute biopsy cost my insurance company roughly about \$750 or \$800.

If it had been done in the emergency room of the hospital, under local anesthesia, the surgeon would probably get \$50, maybe \$5 for the novacaine, and \$10 or \$20 for the use of the room.

I will not say that most surgeons consciously do it for money, although some may. I do not think surgeons are really all that aware of what they are paid. I think it is just a bad habit they picked up.

When I wrote my book, I gave money—the “economic incentive”—a great deal of emphasis. Since then I have talked to so many surgeons who do not even know what they are paid per operation, that I cannot believe they do what they do purely for the money. I think they just do not know any better. But I do not know which I would rather have, a greedy surgeon or a dumb one.

[Laughter.]

Senator KENNEDY. Thank you very much, Mrs. Kushner. It was very, very helpful. Disturbing testimony, but we are glad to receive it from you.

Our second witnesses this morning: Dr. Frank Rauscher, Director of the National Cancer Institute, NIH; Dr. Vincent DeVita, Director, Division of Cancer Treatment at National Institutes of Health; and Dr. Bernard Fisher, professor of surgery and director of oncology, University of Pittsburgh.

Dr. Rauscher, it is nice to have you.

STATEMENT OF FRANK J. RAUSCHER, JR., PH. D., DIRECTOR, NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH; VINCENT T. DeVITA, M.D., DIRECTOR, DIVISION OF CANCER TREATMENT, NATIONAL INSTITUTES OF HEALTH; AND BERNARD FISHER, M.D., PROFESSOR OF SURGERY AND DIRECTOR OF ONCOLOGY, UNIVERSITY OF PITTSBURGH

Dr. RAUSCHER. Thank you, Mr. Chairman.

Senator KENNEDY. You may proceed.

Dr. RAUSCHER. Mr. Chairman and members of the committee, good morning.

I would like to first introduce my two colleagues: Dr. Bernard Fisher, on my right, University of Pittsburgh, Chairman of the National Cancer Institute's national surgical adjuvant breast cancer project, and on my left, Dr. Vincent DeVita, Director of our Division of Cancer Treatment at the National Cancer Institute.

I do have a short statement, Mr. Chairman, if I may, I would like to read it for the record.

Senator KENNEDY. Yes.

Dr. RAUSCHER. Mr. Chairman and members of the subcommittee, thank you for this opportunity to discuss major progress in the treatment of women with breast cancer. The goal of treatment research within the national cancer program is to develop the means to cure as many cancer patients as possible and to maintain maximum control of the cancerous process, including return of the patient to near normal lifestyle and to normal life expectancy. Breast cancer occurs more frequently—that is, after skin cancer—and causes more deaths in American women than does any other form of cancer. It is the leading cause of death among women 40 to 44 years old.

For more than 75 years, the Halsted radical mastectomy has been the standard surgical treatment for breast cancer. Development of

more sophisticated surgical and radiotherapeutic techniques resulted in improved survival rates until about the 1950's. But they have remained relatively unchanged since that time. The reason for the plateau in survival rates is that in most cases, breast cancer, as indeed most cancer, is not a localized disease. Local treatment could cure only those with localized disease.

In the 1950's, investigators began to realize that some systemic form of treatment was necessary to control most cancers. The development of antitumor drugs was begun in the middle 1950's. The first success with chemotherapy was obtained during those years with acute childhood leukemia, followed in the early 1960's by choriocarcinoma, a tumor of the placenta. The drug methotrexate has shown to be effective in the 1950's followed by other drugs in the 1950's and 1960's—curative in certain circumstances, but it has taken some 20 years to bring treatment with drugs to the level of a proven modality for treatment. Immunotherapy, while very promising, is still considered experimental for the treatment of cancers in people.

What we are doing today in treatment research may be viewed as a definitive step in a 75-year experience. This period covers 50 years of development of sophisticated local treatment and 25 years of realization of its limitations and development of systemic treatments.

Today, therapy is highly effective for breast cancer when it is detected as localized disease. The average 5-year survival rate is 84 percent for women in whom the breast cancer is not known to have spread into the axillary lymph nodes. However, too often the cancer has spread beyond the original location, reducing the 5-year survival rate—as was mentioned this morning—to about 50 percent.

There are major new opportunities for significant improvement of survival of breast cancer patients. Progress made in just the last 3 years has provided remarkable new options for effective treatment.

Two large studies have shown that chemotherapy after mastectomy significantly lowers the recurrence rate in women found at surgery to have cancer in adjacent lymph nodes.

The anticancer drug, L-PAM, is an effective postoperative treatment, according to my colleague, Dr. Bernard Fisher, who will talk more about that later.

Senator KENNEDY. In most clinical trials, is it absolutely essential to do away with bias which is built in on the part of physicians in selecting patients by any means other than randomization?

Dr. RAUSCHER. I am sure that with a bias factor, we would not be able to have confidence in our results.

This study, which has been in progress nearly 4 years, includes about 400 women patients in 37 United States and Canadian hospitals. It is a double-blind study, in which consenting patients were randomly assigned after surgery to receive either L-PAM or a placebo: that is, no drug at all. L-PAM was selected because it has minimal side effects and is given orally.

Senator KENNEDY. Results obviously may serve the women of the future better, but I suppose the ethical question is how do you justify the fact that some women will not be receiving what is generally the best known protection at the present time.

Dr. RAUSCHER. Some patients, to be sure, are not suitable for randomization or are not suitable for participating in clinical trial. We believe historical controls are highly protective of patients treated with anticancer drugs. Any treatment given in a clinical trial is as good as the best accepted standards of the day, so we are always adding something on top of the very best known, so a woman is assured of getting what is generally believed to be the best treatment.

In premenopausal women the recurrence rate for those receiving L-PAM was markedly reduced, as compared with the recurrence rate for those who received surgery alone.

This I think, Mr. Chairman, gets partly to your point.

This finding influenced the investigators to make a change in the L-PAM protocol. Starting in September 1974, the placebo was no longer administered to premenopausal women.

Postmenopausal women, in whom results with L-PAM were not as marked in the first report a year ago, are now beginning to show a significant advantage in using L-PAM. The rate of recurrence in this group is one-half of that for women not receiving the drug.

A new study is under way to determine if it is possible to improve on the L-PAM results. It will compare the effectiveness of L-PAM alone with L-PAM plus 5-FU as an adjuvant to surgery in patients whose breast cancers have spread to the lymph nodes.

In a second trial—and this has received some publicity lately—Dr. Gianni Bonadonna and coworkers at the National Tumor Institute, Milan, Italy, reported preliminary findings from a large NCI-supported study of adjuvant chemotherapy. This study is a follow up of the development of an effective combination of three drugs—cyclophosphamide, methotrexate and 5-FU—we call it CMF—begun in 1970 at the NCI under the leadership of Dr. George Canellos. The Bonadonna study is based on the original program designed by Dr. Canellos and his colleagues.

It uses CMF as a program of chemotherapy after initial surgery in breast cancer patients at high risk of recurrence; that is, those with the cancer spread beyond the breast. The patients had been followed for an average of 14 months at the time of the recent report. Both pre- and postmenopausal patients receiving the drugs had a decreased rate of breast cancer recurrence, as compared with a group of women who did not receive CMF. The recurrence rates in the patients receiving CMF were five times lower than those seen in the L-PAM study.

Senator SCHWEIKER. That is not the double-blind study with placebo?

You said you changed the study and eliminated the placebo in that. That is without the placebo?

Dr. RAUSCHER. That was with the original L-PAM study, in premenopausal women. Their data began to look so good after 2 or 2½ years, we thought it was no longer unethical to continue women on a placebo, so we broke the code, analyzed the data, and provided the drug to the other women as well.

Senator SCHWEIKER. This five times lower is based on that change?

Dr. RAUSCHER. Bernie, help me out on that. Is that right?

Dr. FISHER. Yes; this is the Bonadonna study. When we say it is five times better than the original L-PAM study at that time, that is correct.

Dr. RAUSCHER. The results of these two studies are encouraging, and they support the rationale for applying drugs early in the treatment of cancer to destroy tumor cells that may have spread to distant parts of the body. We must allow more years to elapse before we can state with certainty whether we are influencing the survival rate.

Senator KENNEDY. How widely are those results being disseminated?

Dr. RAUSCHER. Very widely indeed, through our 18 comprehensive cancer centers as well as through the many multidisciplinary cancer treatment institutions in the country. Through Dr. Fisher's surgical adjuvant study, results are also being distributed and this mechanism has proven to be very effective.

Senator KENNEDY. What can you tell us about how it is affecting the clinical practice?

Dr. RAUSCHER. Well, we find that more and more women are getting this adjuvant chemotherapy, certainly far more than just a year ago.

Senator KENNEDY. You do not have any way of monitoring how that is being used, where it is being used, and what kind of follow up you are getting? Do you institutionalize that?

Dr. RAUSCHER. We have a very effective way of monitoring that in institutions supported by the NCI through our clinical cooperative groups, through the surgical adjuvant groups, and through participants in our breast cancer program, in general.

Senator KENNEDY. You do that?

Dr. RAUSCHER. Oh, yes, indeed, and through the comprehensive cancer centers as I say.

Senator KENNEDY. Could you submit a brief note on that about what sort of follow up is being done in cancer?

Dr. RAUSCHER. Be glad to do so.

[The information referred to follows:]

Breast Cancer Demonstration and Education Activities
Conducted by the National Cancer Institute

The National Cancer Institute has several activities underway to disseminate information about recent advances in breast cancer therapy.

The Institute, for example, is working with the NIH to develop an hourlong film program to provide definitive information for physicians on breast cancer. It will include sequences developed in several locations, including Bethesda, Pittsburgh and Washington, D.C. The film will be telecast via the Communications Technology Satellite to 10 or more receiving stations across the United States for further dispersal by means of ground communications networks. Videotapes of the program also will be made available to medical schools and hospitals which do not receive the signals directly. Showing of the film to physician audiences will be followed by videotaped grand rounds from the NIH Clinical Center. Questions can be telephoned in by viewers to an NCI panel at the Clinical Center.

A major international conference, called "Breast Cancer: A Report to the Profession, 1976," will be held in November 1976 for members of the medical and health professions. The program has been designed to report and discuss major problems concerning biology, epidemiology, diagnosis, and treatment of breast cancer today.

An active effort of NCI's cancer control division is demonstration programs for various cancer types. These programs involve networks of cooperating physicians and hospitals. One of the networks disseminates the latest information on the treatment of breast cancer. These programs

7/23/76

develop the means to involve local physicians in "full care" patient management protocols. They also consider all interventions: prevention, detection, diagnosis, treatment, rehabilitation and continuing care.

Special grants from NCI to the Comprehensive Cancer Centers of the Nation are enabling the Centers to develop outreach programs in their regions. These programs send out specially trained physicians, nurses, and technicians to deliver information, including breast cancer information, to groups of physicians and hospital staffs through lectures, seminars and special consultations. To date, more than 800 community hospitals have received outreach assistance from the Centers.

Other activities include the community-based programs of NCI's cancer control division. These programs are designed to determine the impact of coordinated control efforts on specific types of cancer, including breast cancer, in a few selected communities of 1.5 to 3 million population. Each community will organize a coordinated effort, with public and professional education components, including medical schools, cancer centers, private physicians, voluntary groups, and state and local health departments.

There is a newly established control effort within NCI's Clinical Cooperative Group Program designed to provide assistance directly to local practitioners. Investigators in this program, which involves more than 400 hospitals, will now be able to devote more time to assisting practitioners in treating cancer patients. The investigators will help practitioners with techniques of administering multi-therapeutic protocols, and provide a broad based high quality transfer of the latest knowledge--including that about breast cancer.

Senator KENNEDY. Do you have any essential feel about how often this model is being used in the noncancer clinical areas?

Dr. RAUSCHER. Yes; we had some feel for this, because each of our comprehensive centers, as you know, Mr. Chairman, is required to have an outreach program. Fifty different hospitals may be associated with a comprehensive center. I do not mean to imply here all women are receiving this treatment yet.

Much of what I presented has to do with the recurrence rates or the number of recurrence rates, and that must be compared inevitably to survival rates. We do not have 5-year data under our belts yet. I think when we reach that point and there are survival data showing significant improvement, then it will be picked up much more widely than it is now.

A number of other drug programs in clinical trial for treatment of recurrent, metastatic breast cancer have produced response rates of 50 to 60 percent in patients with recurrent breast cancer. The effective compounds belong to different classes of anticancer drugs, which have different mechanisms of action in killing cancer cells and thus increase the chances of cancer cell destruction. The drug, Adriamycin, as an example, which has become available relatively recently, has also been incorporated in treatment plans for breast cancer. This drug has been shown to be the most active single agent against advanced breast cancers as well as other cancers.

Another line of research concerns the predictability of the response of breast cancer to hormone therapy. A test has been developed that predicts which patients will respond well to this form of treatment. Presence of a special protein, called estrogen receptor protein, in the tumor predicts that the patient has a good chance of benefiting from removal of the ovaries or other methods of hormone modulation. Its absence suggests that the best prospects for a patient may depend on the use of other treatment, such as chemotherapy already described.

We are also conducting a study of the effectiveness of less radical surgery for breast cancer, with or without postoperative radiotherapy. This study, now about 4 years old, is comparing radical mastectomy—that is, removal of the breast, underlying chest muscles, and surrounding lymph nodes—to total mastectomy, which is removal of the breast only, and total mastectomy with radiotherapy of the chest.

In some 1,700 patients who received one of these treatments, no significant differences have occurred in treatment failure rates or survival. The results suggest that less radical surgery may be as effective as the traditional radical surgery.

Senator KENNEDY. Based upon the studies that have been done, can you draw that conclusion now?

Dr. RAUSCHER. Yes, sir, we are drawing that conclusion now.

You know, these studies take 5 years or more, and this is now 4 years underway. To date, there is no apparent advantage by comparing radical with the modified radical.

Senator KENNEDY. You would rather wait until the full clinical trial is completed, but based upon the 4 of the 5 years, this is your considered judgment?

Dr. RAUSCHER. That is correct. And this is compatible with data from other countries as well; I think this is the most definitive trial so far.

Senator KENNEDY. That has taken place?

Dr. RAUSCHER. Yes.

Senator KENNEDY. Now, if this is your conclusion, what are you going to do to get that information out to the practicing physician and surgeons in this country? What are you going to do to get it out to those clinical centers, and how are you going to make that particular option available to the American women?

Dr. RAUSCHER. Once a trial is complete, the data speak for themselves. I have no doubt about this. It is very easy to get this information out through our comprehensive centers and institutions of the type that are known to deal predominantly in cancer treatment. That is no problem. It will go out very quickly.

The other way to do it is to talk to people like Dr. Fisher, to cancer surgeons, and go to the professional societies in the country, or go to the American College of Surgeons and provide that information.

Senator KENNEDY. If your wife had cancer of the breast, which would you advise here?

Dr. RAUSCHER. I would advise her to have a modified surgical procedure followed by chemotherapy.

Senator KENNEDY. I think all of us are impressed by the leadtime that is necessary to get doctors to alter a change in the procedures which they follow over the years. This is something that is terribly, terribly important. What do you think is the best way of doing it?

What can be done to really educate the American surgeons about this? And also educate the American women to these two alternatives, radical mastectomy—

Dr. RAUSCHER. The best way to educate them is to present them with definitive data, based on trials with adequate numbers of people for an adequate length of time.

Now, there will still be surgeons who honestly believe that procedure A is still better than procedure B, and I think this is why the former witness said 19 surgeons disagreed. It is because they honestly believed the Halsted radical was better. We have got to provide the kind of data we are about to.

Senator KENNEDY. Should the consumer bear the burden because some doctor is not personally satisfied? Is the consumer going to be the sufferer because some particular doctor has got a quirk in the back of his mind and thinks it ought to be done? He does not suffer; it is the woman who suffers. How are we going to alter or change that?

Dr. RAUSCHER. Again, we have not done so thus far; there has been controversy because we really did not know, but now that this particular study comparing three lines of this surgery protocol is coming to an end, I think the data will be convincing.

I think the physician is right to want to see this study finished—a definitive study with good 5-year data. We prefer more than that, but with good 5-year data, we should be able to convince him.

I think your other point is just as important, Mr. Chairman, and that is you ask how do we convince the layman, the women in the country. Most of us spend a great deal of our time giving interviews to newspapers, speaking publicly on television—I presented 50 lectures at least last year myself to ladies' groups, to lay groups; that is the way to do it. So that they can demand the very best.

Senator KENNEDY. I hope when this is finalized and in your information program, that you can think of ways we in Congress can be helpful either through legislative ways or additional support for the program. I hope you will let us know.

I think what is always going to be lingering in my mind is even after you have gotten this firm and definitive information and have published it, you are going to find that a doctor in someplace is not going to take the time to read it, or if he does read it, still is not going to be convinced about it, and the person who is going to suffer is going to be the woman.

I think we have to really explore every kind of possibility to make sure that that is not the case. We want to work with you.

Dr. RAUSCHER. We certainly will.

Senator KENNEDY. How much time, Doctor, do you need to complete this study?

Dr. RAUSCHER. Well, most people would like to see at least 5 years' survival data. So I think that is the most direct answer to your question.

Senator SCHWEIKER. Now, I remember when you folks came to us in 1974 and wanted to break the code and abort the study then, that's the L-PAM protocol you just mentioned, because you thought there was a significant breakthrough.

Dr. RAUSCHER. Yes.

Senator SCHWEIKER. You sort of violated the rules of the game.

Dr. RAUSCHER. That is right.

Senator SCHWEIKER. My only question is, if we are at the point where the data is fairly convincing and women are still going out and getting radical mastectomies, should we not be thinking about doing the same thing here?

Dr. RAUSCHER. It is a bit different. Based on historical controls, comparing what we know about the kind of cancer patients going into those first L-PAM trials, we were quite convinced that the very remarkable improvement in nonrecurrence rates would persist. Because we had 2 to 2½ year data as I recall at that time, we thought we were obliged to take those women off placebo.

But in terms of survival, the longer you get away from the point of value in surgery, the greater are the chances, of course, for recurrence. So that you would expect more recurrences by far in the fifth year than you would in the first year. And because of that kind of accelerating recurrence, I believe it is very wise to really get these data for the first time in 75 years and wait that 1 more year.

Senator SCHWEIKER. Now, one followup question. Suppose the results come out as you expect they might, what steps beyond what you told Senator Kennedy might we take if results are as good as we hope they might be in this area to get to the doctor who still wants to do it the old way and does not give the woman much choice?

In other words, I think that is a pretty basic issue, too.

Dr. RAUSCHER. I think physicians, most physicians, when they see something as good as this, with an adequate clinical trial, will accept it. I think more and more, because of our comprehensive cancer center network, physicians at the community level in community hospitals are seeking advice from physicians in the comprehensive center.

More and more, I think, physicians are recognizing that cancer medicines are disciplines unto themselves; they are very specialized. Therefore, they are more apt to refer patients into a center or into some facility known to have a clinical oncologist or oncologic surgeon.

I think in addition to what I mentioned to you, Senator Kennedy, things like the PSRO program will begin to do far better in assuring that best technology is used by physicians. The National Cancer Institute, for instance, is sponsoring some training, certain education programs at the medical school level, so that physicians coming out would be far more aware of what can be done than their predecessors did just 5 or 10 years ago.

Senator SCHWEIKER. What does this study say about radio-therapy? You did not mention that. In other words, it is a three-part study, total, radical, and total plus radiotherapy.

What is the study indicating on radiotherapy?

Dr. RAUSCHER. I would like to be accurate on this.

May I ask one of my colleagues to respond to that?

Dr. Fisher.

Dr. FISHER. Yes; I will mention this in my statement, but there is no difference at the present time in the three treatment groups, those that have the total mastectomy, those that have the total plus radiation therapy, and those that have the modified radical.

Senator SCHWEIKER. I wonder, Doctor, I know you are very experienced in this area, maybe you would like to answer the other question I just asked Dr. Rauscher about?

Suppose the study comes out along the lines we are talking about now, how do we get some of your colleagues to accept the findings in terms of the three options?

Dr. FISHER. Well, I think it is pretty much like all medical procedure, peer pressure.

Senator SCHWEIKER. That is the trouble.

Dr. FISHER. Peer and patient pressure, plus education.

I think all mechanisms that Dr. Rauscher has mentioned, but there is one more mechanism that exists today, that is the lay press, and this plays a tremendous role in influencing what the physician does.

Senator KENNEDY. Before leaving this particular point, and I think all of us have to be very much encouraged by the preliminary results of the study, what can you tell us, Dr. Rauscher, about what dangers you think are possible for the women who are taking the chemotherapy, the L-PAM and the danger of possible development of leukemia as seen in the course of laboratory testing?

Dr. RAUSCHER. I think there are two things here. These drugs can be difficult to administer as effectively as they can be by the most skilled chemotherapists, so the physician must be aware of how to monitor the patients for the immediate toxic effects of the drug: Hair loss, gastrointestinal upsets, and the like.

Long-term effects, however, are also important, and you have referred rightly to them. We have good reason to believe that drugs like L-PAM may in themselves be weakly carcinogenic. We have known for sometime that L-PAM and related drugs are capable of inducing tumors in animals. It depends on the dose administered and the animal used. But cancers do occur in animals treated by the drug at a higher level than in control animals.

There is reason to believe, therefore, that a small number of secondary/primary tumors may occur in people treated with these drugs. But it is nowhere near the number of the people that we know will be benefited by the drug. The incidence in fact is very, very low. But it is something to be concerned about, you are quite right, and this is why through our drug development program, we continually try to synthesize new drugs that have high anticancer activities, but without any of the side effects, or at least with lower side effects. We are very much aware of this, Mr. Chairman.

Increased intrumural program emphasis has led to the establishment of a new NCI unit to conduct clinical research on all aspects of breast cancer. The research will span early detection, primary surgical treatment, and chemotherapy programs for treatment of metastatic disease.

The cancer control program is supporting demonstration projects involving networks of cooperating community physicians and hospitals linked to major hospitals to disseminate the latest information and techniques in the detection, diagnosis, treatment, continuing care, and rehabilitation of breast cancer. Twelve networks are being developed by 12 institutions in 11 States from New England to California.

The anchor for breast cancer research nationwide is the NCI breast cancer task force program. Its objectives are to expand knowledge of the causes of breast cancer, to develop improved methods for detection and diagnosis, and to develop even more effective treatments.

In summary, Mr. Chairman, multifaceted research is in progress in early detection, diagnosis and treatment tailored to the individual patient.

Senator KENNEDY. Just on that point, what do you think should be the role of the patient in making a decision or determination as to what kind of treatment that they are going to receive?

Dr. RAUSCHER. I certainly think, and I believe are, most of the patients have to be fully informed as to what the various options are.

It depends certainly on the health of the woman at the time she presents. It would depend to some extent on her age, on her place in society I would suppose, as she sees it. I cannot—

Senator KENNEDY. You favor support of the full information being available to the patient, the range of different alternatives, the benefits that may attend by a particular procedure or the potential dangers in others?

Dr. RAUSCHER. Indeed. Absolutely strongly committed to the extent of encouraging a patient to seek a second opinion as an example.

We got many calls, for instance, after an article appeared in—

Senator KENNEDY. You would advise that any patient that received information—

Dr. RAUSCHER. Indeed I would.

Senator KENNEDY [continuing]. On the potential surgery that be advised, receive additional—

Dr. RAUSCHER. That is right.

About four weekends ago an article on cancer came out in one of the Sunday supplements and Dr. DeVita was quoted, and my office has received about 34,000 letters in the past 3½ weeks, most of which

are from patients asking questions just like this. So we would also encourage physicians to call us directly. They do so all the time.

Senator SCHWEIKER. What about the issue of separate biopsy that we were talking about with the other witness? How does that in your judgment—is that a practical, feasible approach or how would you evaluate the separate biopsy?

Dr. RAUSCHER. Again to be accurate, I would prefer one of my medical colleagues to answer.

Vince?

Dr. DeVITA. Yes; I think it is a very feasible approach to do a biopsy first, allow the patient to wake up if she is under anesthesia, or do a biopsy under local anesthesia, then allow the patient to make a decision at a time they know they have cancer, rather than when they are banking on that they do not.

Senator KENNEDY. Dr. Fisher, maybe you want to comment on that, too?

Dr. FISHER. I would certainly think that again after the patient is fully informed, she be given her choice. There is no scientific reason why a patient could not have a two-step procedure.

Senator KENNEDY. Well, what percent have it now and what percent could not have the two-step procedure?

Dr. FISHER. Well, I think it is difficult to put in terms of percentages.

Based upon my own experience I think that there is an increasing number of women who want to have a two-step procedure, but, on the other hand, the vast majority in my experience still prefer to have the definitive procedure carried out at the same time giving as the reason that they do not want to have two different emotional ordeals, two different anesthetics, what have you.

Senator KENNEDY. Do you know as a fact that is the case?

Have you done any kind of study?

Dr. FISHER. No, sir.

Senator KENNEDY. Do you not think it would be worthwhile to know whether people want the one step or the two step? Do you not think that that would be useful, worthwhile to know about?

Dr. FISHER. Yes; I suppose so. [Laughter.]

I think it is important that they be given the option.

Senator KENNEDY. Is there no collection of information that could tell us what the attitude of women on this particular issue? Or what percent are opting for the single versus the two step for that kind of procedure. Do we not know that?

Dr. FISHER. No, sir.

Senator KENNEDY. Even though from a medical point of view there is only a relatively small number that, because of medical reasons, would have to have the single step procedure, am I correct?

Dr. FISHER. Yes; if a woman has an out and out diagnosis of a breast cancer by variety of means, then if there is proper information to this woman, there is little reason to do the two-step procedure.

Senator KENNEDY. Let me ask you, in the public information aspect of the cancer, would not just outlining those kinds of procedures, trying to get that kind of information available to women of the country, would that not be of use and productive?

Dr. FISHER. Yes, I would agree.

Senator KENNEDY. Do you have such a publication now, Doctor?

Dr. RAUSCHER. Yes; we have pamphlets we send out by many thousands, of course.

Senator KENNEDY. I am sure of that.

Dr. RAUSCHER. I have talked to these points in articles in Parade magazine, women's magazines.

Senator KENNEDY. I would think it would be the doctors who would need some talking with in this respect as well.

Dr. RAUSCHER. Yes, sir.

Senator KENNEDY. Well, perhaps you could just let us know on this particular point.

Dr. RAUSCHER. All right.

[The information referred to and subsequently supplied follows:]

TREATMENT OPTIONS AVAILABLE TO WOMEN FROM THE
NATIONAL CANCER INSTITUTE

For the general public, NCI has prepared new projects which are aimed at letting women know that there are treatment options. These projects include activities which have resulted in extensive press coverage of advances in breast cancer therapy, newly developed television and radio spots, television talk show appearances by NCI staff, and a currently underway revision of printed materials related to breast cancer and designed for the public.

Senator KENNEDY. What you are doing, what you think can be done. I think this really is very important.

As you remember, we had an amendment, I think it was Senator Bayh's a year ago trying to expand the whole public information prevention aspect on cancer, but he was not successful because the point was made that we are getting that information and education out to the public and I think we constantly have to ask ourselves whether we are getting the information on it.

Dr. RAUSCHER. We spent a good deal of effort in the past year, Mr. Chairman, on getting information out to the public in various ways.

Senator KENNEDY. I am sure you wish a lot more was being done in all of these areas.

Dr. RAUSCHER. Indeed.

Senator KENNEDY. I think we want to at least be reflective of the kind of interest that we are receiving from an awful lot of people.

Dr. RAUSCHER. I understand.

Senator KENNEDY. Thank you.

Dr. RAUSCHER. If current results continue, the outlook is optimistic for increased use of less radical surgical procedures.

Mr. Chairman, this is major progress, but it could take another 10 years to determine the best role of the various treatment techniques to produce most cures with a minimum of surgery.

I want you to know that the news, so far, is very good indeed. This progress in the treatment of the most prevalent and feared cancer of women results from an evolutionary accrual of research going back many years. It is also true, however, that the results I am reporting now are available today because of the national cancer program, and its initiation and continued support by the Congress since 1971.

Finally, this relatively new technology of combining different methods of treatment for the benefit of the individual patient—based on the

recognition that a majority of all cancer patients have disseminated disease at first detection and diagnosis—is already being applied to patients with other major cancer killers, such as cancer of the lung, colon, and ovary, and we believe with more success than ever before.

Thank you very much, Mr. Chairman.

Senator KENNEDY. Dr. Fisher.

Just before we get started on a matter that was raised earlier by Dr. Rauscher in terms of the study, I think it was drawn to our attention about the question of the adequacy of consent on that double-blind study. I think this is something that you are familiar with, and perhaps during your comments you have made some comment about it, as you well know, with the protection of human subjects issue—a lot of work on the area of consent, you know, we are interest in—and I think it would be useful just in your comments if you, at the end or at an appropriate place in your comments, you could perhaps talk about that issue.

Dr. FISHER. Thank you, sir, Senator Kennedy and Senator Schweiker.

I am grateful for the opportunity to present the following information.

During recent years, there has occurred controversy and even confusion in the United States and the rest of the world relative to the proper treatment of women with primary breast cancer. Whereas, for 100 years radical mastectomy was—perhaps for want of a viable alternative—virtually unchallenged and accepted as the standard and only therapy for the disease. Women with breast cancer today, as you have heard, may have one of a variety of surgical procedures, extended or superradical mastectomy, or a breast-preserving operation known as segmental mastectomy or “lumpectomy”—the choice depending upon the convictions of her physician.

Unfortunately, more often than not, the decision regarding which operation to employ has been based upon information obtained from retrospective analyses of heterogenous case records, the comparison of data not comparable because they were obtained from dissimilar groups of patients, peer pressure, emotional factors, and most importantly, an outmoded concept of tumor biology. Relative to the latter, it is necessary to point out that when consideration is given to recent advances and progress made in the treatment of cancer, little attention is directed toward changes occurring which are as profound and far-reaching in consequence as any in our time. There is taking place a redefinition of the basis for cancer surgery so that it is in keeping with present understanding of the disease.

I have repeatedly emphasized that despite a plethora of publications, it has not been clearly demonstrated that any of the alternative surgical procedures should or should not supplant radical mastectomy. This is not to say that such operations may not produce as good results; well they might. Disquieting as it might be, however, adequate data is not yet available to justify definitive conclusions in that regard. The reports of a host of investigators concerning simple mastectomy, modified radical mastectomy, and so forth, I think have resulted in senseless and uncalled-for polemics.

These investigators have, as a result of retrospective analyses of their experiences, provided suggestive evidence—and I underline the

word "suggestive"—that other surgical modalities may be equivalent to radical mastectomy. The resulting controversy is primarily due to failure to view those studies in proper perspective. The trouble is not so much with the studies as with those who have ascribed more validity to them—positively or negatively—than they deserve, by failing to recognize their purpose and limitations. Such retrospective analyses provide valuable clues and hints of possibly beneficial therapies which require further evaluation. As a result of such suggestive evidence which in itself is not conclusive, it becomes appropriate to obtain definitive data through properly conceived prospective clinical trials.

Now, recognizing the need to obtain objective, unbiased information as rapidly as possible concerning the worth of the spectrum of treatments, the national surgical adjuvant breast project was organized in 1957. Its efforts have been supported by both the clinical investigations branch cooperative group program and the breast cancer task force of the National Cancer Institute. Over the years, surgeons, radiation therapists, medical oncologists, and pathologists—several hundred in number, from more than 50 institutions, who are members of the group—have utilized explicit protocols to carry out clinical trials. Those efforts have not only provided credible data regarding the worth of certain treatments but have also made available a repository of information concerning the natural history and certain biologic parameters of breast cancer previously unavailable.

Appreciating the surgical dilemma, after almost 10 years of planning, a clinical trial was begun in September 1971 by the group to compare, as you have heard, the results of radical mastectomy to those obtained following a lesser procedure, total—sometimes called simple-mastectomy, with and without postoperative radiation. It is emphasized that strict guidelines for patients acceptance into this and all protocols are rigorously adhered to. By August 1974, when patient accrual was terminated, almost 1,700 patients were entered into this evaluation. The average followup time is now almost 30 months and to date there are no significant differences in results between the treatment groups. It cannot be too strongly emphasized, Mr. Chairman, that such results must be considered provisional. With each additional time period that elapses, they become more definitive. That study will answer important biological questions as well as indicate whether the lesser procedure being tested is or is not equivalent to radical mastectomy.

Now, because of the preliminary findings of the aforementioned trial and because of evidence from a variety of uncontrolled studies to suggest that segmental or lumpectomy might or could be appropriately employed in the management of certain patients with breast cancer, and since patients throughout the world have been and are being subjected to that operation, it was deemed mandatory that a clinical trial to confirm or repudiate the worth of that procedure be carried out at once. More precisely, it has been determined that there is more justification for carrying out such a trial than for not doing so. Consequently, a protocol has recently been implemented which compares segmental mastectomy with or without breast radiation to total removal of the breast. The aim is to obtain definitive data to affirm or deny the worth of breast preserving operations for breast cancer and

to answer the question, "Can better cosmesis be obtained with no additional risk to the patient?" All patients will have their axillary lymph nodes removed and those having tumor in them will receive systemic chemotherapy. It is emphasized that segmental mastectomy is applicable only to a portion of patients with breast cancer; that is, those with small tumors who have ample breasts so that a segment may be removed while at the same time a reasonable cosmetic result is achieved. Whether or not that trial may be carried out successfully in this country depends entirely upon the willingness of patients and their physicians to participate in the evaluation. If they are not willing to do so, the arguments will continue and the answers will remain unknown. Thus, Mr. Chairman, there does exist a mechanism and a plan to obtain data objectively and without bias to resolve the surgical dilemma.

Now, Mr. Chairman, I should now like to turn attention to another aspect of the breast cancer problem. Increasing evidence indicates that most, if not all, patients with breast cancer have disseminated disease at the time of diagnosis. Operation alone all too frequently is inadequate to effect a cure. This is substantiated by treatment failure and survival data obtained 10 years after the first NSABP trial and recently reported by our group. Particularly distressing was the finding that 75 percent of patients with histologically positive axillary nodes and 25 percent with negative axillary nodes treated by radical mastectomy alone had a treatment failure. There is increasing receptivity to the consideration that improvement in survival will result only from the employment of effective systemic therapy in conjunction with modalities, surgery, and radiation, employed to control local and regional disease. This systemic treatment has become known as "adjuvant therapy."

In order to prove the concept of the worth of adjuvant chemotherapy, a systematic "game plan" was established by the NSABP. It was to begin by evaluating the worth of the prolonged use of a single agent, L-PAM, which had relatively little toxicity, could be easily administered, and would be readily acceptable to both patients and physicians. Moreover, there was reason to anticipate some modest improvement in results by the use of that drug. The plan was to proceed in stepwise fashion progressively evaluating more complex combinations of drugs so that it could be eventually ascertained what the minimal treatment need to be obtain maximal benefit in terms of freedom from disease and survival and, at the same time, produce the least undesirable side effects to the patient.

In the winter of 1972, a clinical trial in women at great risk to do poorly following operation alone; that is, those with positive lymph nodes, was begun and the results have been widely publicized subsequent to a report of early findings in 1974. Information from 400 women on study still indicates that the drug significantly prolongs the disease-free period of women, particularly those who are premenopausal, and accomplishes this with minimal undesirable side effects.

With completion of patient entry into that trial, and in keeping with our original plan, a new evaluation was begun in February 1975. A comparison was made of the single agent L-PAM to the combination

of L-PAM plus 5-FU. Seven hundred patients have been entered into that evaluation in 1 year and patient entry has been terminated. Since there is only an average followup time of 6 months, it is too soon to have meaningful data. The toxicity of the two agents, while greater than with L-PAM alone, is quite acceptable in the adjuvant setting.

Once again, in keeping with our original approach, 2 weeks ago we began a new protocol which evaluates the effects of the two-drug combination, L-PAM plus 5-FU, with a three-drug combination, L-PAM plus 5-FU plus MTX. Other protocols to be implemented in the future by our group will evaluate the effectiveness of immunotherapy in combination with chemotherapy and the combination of chemotherapy with certain hormonal agents.

In retrospect, the results from the L-PAM study and those by other investigators, extend and support our original observations obtained from a clinical trial begun in 1958 that a short postoperative course of ThioTEPA was effective in reducing the treatment failure rate and improving survival of a subset of premenopausal patients for at least 10 years, providing the first evidence that such adjuvant therapy might be meritorious.

What is the significance of the recent findings? How do they affect current management and how will they influence future therapeutic strategies? Their greatest importance is that for the first time it has been demonstrated from a well-controlled clinical trial that the rationale for using prolonged chemotherapy as an adjunct to operation is a sound one. Different agents, multiple agents, refinements of administration will undoubtedly produce better and better results. This will follow as a corollary to these observations, but to the initial steps forward have been achieved.

Moreover, these findings and others with adjuvant therapy devalue all previous arguments relative to the worth of one surgical procedure versus another. As systemic therapy becomes more effective, the more likely it becomes that lesser operative procedures will be comparable to those which are more expansive. As a consequence, increased disease control may be accomplished together with better cosmesis. It is not unreasonable to anticipate that the use of systemic therapy will make remote the chance that a lesser surgical procedure will put a patient at a disadvantage. In our opinion, as result of the findings, evaluation of segmental mastectomy is more appropriate than ever.

There would seem to be justifiable reason for optimism concerning the future of women who develop breast cancer. There can, however, be no permanent prescription or recipe for the management of this disease simply because progress is proceeding in various directions with increasing momentum and it is impossible to predict the ultimate nature of the next plateau. Moreover, in my opinion, adjuvant therapy for breast cancer as of May 1976 must still be a component of clinical research in oncology.

In conclusion, it is imperative that if progress in the resolution of this therapeutic dilemma is to proceed rapidly there must be more universal acceptance by patients and physicians of the clinical trial mechanism. It is imperative that patients and the public at large be

made aware that there may be alternative methods of treatment, that there may be legitimate uncertainty as to which is best, that properly formulated clinical trials can help to resolve this uncertainty, and that such undertakings are an ethical facet of modern medicine. Physicians who care for such patients must be prepared to accept and promulgate clinical trials so that therapeutic modalities may be evaluated prior to their employment on the population as a whole. They must, in addition to giving their patients the best available treatment, accept the responsibility for helping to ascertain what best treatment is.

Finally, more adequate resources must become available so that additional clinical trials may be promptly carried out. To continue to prolong such therapeutic uncertainties as mentioned here, decade after decade, is a disservice to patients with breast cancer.

Thank you, Mr. Chairman.

Senator KENNEDY. Thank you, Dr. Fisher. How did you get volunteers to participate in this program?

Dr. FISHER. A protocol was established by the membership of the national surgical adjuvant breast project, which, as I have said, consists of a multiplicity of institutions, medical centers, cancer centers, and hospitals in this country, and the physicians who participate in this study are truly those who do not know what the best answer is. If a physician does know what the best answer is, he is not in the best position to do a clinical trial.

When a patient presented herself to those physicians, she was presented with the kind of information that I have presented here today, and was asked whether or not she would be willing to participate in such a clinical trial—and she was a volunteer for such a trial. She was given the free right to accept or not to accept, she was given no incentive for accepting or not accepting, and she was given the total permission to withdraw at any time or to pick any other treatment, or she was informed that should some other treatment become necessary, other than that which would be selected in the clinical trial, she would have that treatment.

Senator KENNEDY. How many did you ask and how many turned it down, do you know?

Dr. FISHER. The majority of women accepted this. I cannot give you the exact figure; I do not have that.

Senator KENNEDY. Could you provide that for us?

Dr. FISHER. I could try.

Senator KENNEDY. How many dropped out during the course of the study?

Dr. FISHER. Very few.

Senator KENNEDY. Could you provide that for us?

Dr. FISHER. Yes.

Senator KENNEDY. Did you, during the study itself, feel that it was necessary to provide additional information to any of the volunteers about the various strengths or weaknesses of the different treatments that they could have been receiving during this period?

Dr. FISHER. Yes, sir, absolutely.

Senator KENNEDY. And how often did you do that?

Dr. FISHER. All the time.

Senator KENNEDY. What did you do all the time?

Dr. FISHER. Patients were informed before they entered the study as to what the alternatives were, as to what the complications of each of the procedures might be, as to the possible—that we didn't know what the long-term effects were, and the possible risks.

This was part of her informed consent.

Senator KENNEDY. Was that written down in some form that was made available to them to sign?

Dr. FISHER. Yes; it was.

Senator KENNEDY. Would you submit that to us, too?

Dr. FISHER. Yes.

Senator KENNEDY. Was that ever changed or altered as it went through?

Dr. FISHER. Yes.

Senator KENNEDY. Could you provide us the modifications that were included in the profile, in the study?

Dr. FISHER. Yes.

Senator KENNEDY. How was the extent of the original surgery decided?

Dr. FISHER. A strict, rigid set of guidelines existed in the protocol for classifying a patient, according to the extent of her disease, relative to the pathology of her disease, relative to the clinical findings, relative to laboratory studies. Having done this, such a patient, then fell into a category where she may very well have had either one of the treatments suggested without there being any reason why she could not.

Senator KENNEDY. You mean guidelines were developed, given the nature of the various diagnoses about the extent of any surgical procedure that would be practiced on any of the volunteers?

Dr. FISHER. Yes.

Senator KENNEDY. I am just wondering, you know, the extent that women or others are prepared, in this area, to be willing to participate in such a program, the problems that you are facing in getting volunteers—and obviously I am very interested in assuring that any one that does volunteer—as I am sure you are, Dr. Rauscher and the others in the program want to make sure that the full range of information is available to any of the people that would participate in the program.

Senator Schweiker?

Senator SCHWEIKER. Doctor, I would like to follow up a little bit on the technology here that you outlined, which I find very intriguing.

I gather, first of all, the NCI has found two encouraging lines of chemotherapy, one relating to L-PAM and the other to the Bonadonna study with CMF. Basically, they are two of the more promising aspects of your chemotherapy, is that correct?

Dr. FISHER. Yes, sir.

Senator SCHWEIKER. Then, as I understand what you are saying in your testimony, you are trying to combine these elements in some protocols. As I understand your latest protocol, you are taking two of the drugs in CMF and combining it with L-PAM; is that basically what you told us?

Dr. FISHER. Yes.

Senator SCHWEIKER. All right, I also gather from that that, because you took L-PAM plus 5-FU, that it was indicative that it might be a

more promising path than others which you took, and the fact that you are then adding a second ingredient from CMF indicates that might possibly have even more interest—is that pretty well the logic and reasoning as to why you are going—

Dr. FISHER. Yes, sir.

Senator SCHWEIKER. Now, let me ask a layman's question. Obviously we have some encouragement here and I think some significant developments in chemotherapy. Do we understand why at this point, or is this like a lot of our discoveries, that we just know is works better? Can anybody explain in layman's terms as to why we expect this line of pursuit of chemistry to work, what's happening here—or don't we know that yet?

Dr. FISHER. I think we have a very good idea, sir. I think it's very important to emphasize that for many years the clinical cooperative program in this country has been evaluating combinations of chemotherapy in patients with advanced breast cancer, and has gotten important leads, has been able to improve survival and get regressions in patients with advanced disease.

And what we have really done now is to take those modalities which have been found effective in advanced disease and to use them earlier in the patient's history. As I said, we believe that most patients with breast cancer do have disseminated disease at the time of surgery. But the burden of tumor cells which is left behind, following removal of a primary tumor, is much less—is less than at any other time in the subsequent history of that patient.

Therefore, the time to destroy those cells most effectively would be early on. And while we have found out, for example, that three drugs or four drugs in various combinations are much more effective in advanced disease than one or two drugs, this has never been shown for early disease. In other words, maybe in advanced disease it takes three drugs, but maybe one drug could do the job in earlier disease because of difference in number of tumor cells present. And it's cell kill, tumor cell kill, which is the mechanism by which this has taken place.

Senator SCHWEIKER. One other layman's question. What would be the likelihood of combining both L-PAM and the three ingredients of CMF in some test, or is this not a logical thing to do?

Dr. FISHER. Well, it really is not, because L-PAM and cyclophosphamide are similar drugs. They are called alkylating agents, and they behave in similar fashion.

Senator SCHWEIKER. So you have taken two of the three that are not similar.

Dr. FISHER. That's right, sir.

Senator SCHWEIKER. How far down the road—I realize that the latest protocols are very new—in terms of the last one which you outlined, which is a combination of L-PAM and two of the CMF ingredients, how long will it take us? Is this a 5-year study, or how far down the road?

Dr. FISHER. Well, sir, it depends on how rapid there is patient accrual in a clinical trial. I have said that in order for a clinical trial to be most effective and to give us the results in the quickest time, we must get a bolus of patients into a trial early and as quickly as possible.

If it takes 3, 4, 5, or 7 years to accrue patients into a clinical trial, then it is going to take infinitely longer to get the results. But if all of the patients that we would need to give a significant answer could be entered on day 1, then the results would become increasingly more rapid.

So the mechanism of the trial, to some extent, determines the rapidity by which an answer is obtained.

Senator SCHWEIKER. Wouldn't it be true that because of some of your early success here with these two lines of inquiry, that that would also help your accrual problem somewhat, just by the fact that—

Dr. FISHER. It has, no question about it! As I mentioned, we accrued 700 patients in 1 year with the L-PAM plus 5-FU, whereas it took about 3 years to get 400 patients in the previous trial.

Excuse me, Dr. Rauscher has brought up the point that needs to be mentioned, and that is that this is an international cooperative venture. Institutions from Canada, from Europe, are also participating.

Senator SCHWEIKER. I would like to ask Dr. Rauscher a question, a little different line of inquiry.

Doctor, do we have any kind of cancer registry, or is there some kind of scorekeeping apparatus whereby we are making note of what has been happening and the kind of treatment women are getting and what we are experimenting with, other than just the contracts that NCI makes, which obviously you would keep score of?

Dr. RAUSCHER. We have some excellent cancer registries in the country. You may recall, Senator Schweiker, just a few years ago we completed what we called our Third National Cancer Survey to determine health practices regarding cancer in the country, to determine incidence, morbidity, and mortality.

So we do have a very effective means at different locations in the country, now—10 different areas—in determining trends in survival and incidence.

Senator SCHWEIKER. Does this get into everyday-practice kind of things where—or is this a matter of where we are lining up a survey and specifying it, or is there also an element of actually finding out what is going on in everyday treatment?

Dr. RAUSCHER. A very important element—at various places in the country, again—of finding out what is going on day by day. It is not a specific project for a specific purpose, but rather an ongoing surveillance mechanism.

Senator SCHWEIKER. Within that given area?

Dr. RAUSCHER. That's right, and we have the entire United States, Puerto Rico, Hawaii, represented.

Senator KENNEDY. Well, I want to thank you very much. Dr. Rauscher, we are glad to see you here; appreciate very much, as always, your presence here and the work that you do on this program.

Dr. RAUSCHER. Thank you, sir.

Senator KENNEDY. And we thank your associates as well—very, very helpful, and I think any time that you talk about these issues, you bring not only your own very considerable talent and expertise, but I think it is enormously useful and helpful to the American people to understand what is happening out there.

Senator SCHWEIKER. And I think it's very encouraging. We sit through a lot of these hearings, particularly in the Appropriations—Labor, HEW—and spend a lot of money. You don't know if it is well spent. It is certainly good to hear—you have got some good news for us, and you are making some progress, and we see a little bit of light around the corner.

So we certainly feel good about that. We appreciate that.

Dr. RAUSCHER. Thank you. I have never been more proud of any finding, more proud than of this one. You know, the incidence is exceedingly high, and I think the results are quite remarkable.

Senator KENNEDY. Very good. Thank you very much.

**STATEMENT OF GEORGE CRILE, JR., M.D., EMERITUS CONSULTANT,
DEPARTMENT OF GENERAL SURGERY, CLEVELAND CLINIC**

Senator KENNEDY. We have two more witnesses. Dr. Crile is a graduate of Yale College and Harvard Medical School, has been with the Cleveland Clinic since 1934, and he is now emeritus consultant with the Department of General Surgery at the Cleveland Clinic.

We want to welcome you, Dr. Crile. We are looking forward to your testimony.

Dr. CRILE. Mr. Chairman, with your permission, I would like to deviate from my prepared text, much of which has been covered in previous discussion. Is that acceptable?

Senator KENNEDY. It is. We will include your prepared statement at the end of your testimony.

Senator SCHWEIKER. Commendable.

Dr. CRILE. I would like to make this quite informal and to discuss some of the points that Senator Kennedy has raised. For example, about women's choice as to what operation they would have. There is no predicting this. We have had wide experiencing with offering, in selected cases, partial mastectomy to women, if the tumor is small and peripheral and the breast is ample, so that it can be reconstructed.

But yet the pros and cons of this are discussed thoroughly with the women, a great many of them—perhaps 40 percent—will opt against the mastectomy.

Oftentimes a young woman, with a family of young children, will just want to do the safest thing in the world—she is solidly married, she doesn't care about losing a breast, and she will opt for a mastectomy—and she should certainly be encouraged in that, because the more breast tissue you remove, the less chance there is of getting further breast cancer.

Some older women, no longer sexually active, just say they don't want to worry about it—they want to live to see their grandchildren grow up—you do what you think best, doctor.

Then there is the group in between. You have the women, many of them divorcees and so forth, to whom the breast is extremely important in their sexual-social life, and these women, I think, should indeed be informed that a partial mastectomy can be done with a great deal of increased risk as far as local recurrence is concerned, but no difference at all in the long run in terms of survival.

So that is the kind of decision that is very hard to make. I think that a trial can be done with these things in such a thing as mastec-

tomy versus partial mastectomy, because different women will opt for different types of operations.

Now, there was a long discussion about biopsy, and no mention was made about the office procedure which is so common in Europe, and Scandinavia particularly, of the aspiration biopsy of the tumor. We routinely, when a woman comes in with a lump in the breast, aspirate that with a very fine needle, a 20-gauge needle. This gives you a cytology preparation just like a pap smear. And this is highly accurate, about 90-95 percent accurate. You would not necessarily take that as a final diagnosis, but if you do this routinely, of the women that you are going to subject to—you are still going to have to do an open biopsy if there is a mass there. But you can tell the women that you have, if that is positive, that you have a 95-percent chance of this being cancer, so we might just as well do this whole operative procedure, frozen section and everything, at one stage.

But the others, if the smear has been negative, it is very rare that you find a cancer there—perhaps not 1 in 20. So you don't have to frighten all those women getting them prepared for a mastectomy, if it is. You say, we do this as an in-and-out, it's a great economy, we don't have to put her through all the preoperative tests that you would for a mastectomy.

So I really think—we are moving rapidly in that direction in this country, and I think that within a few years this will be a widespread technique.

As has been brought up right along, the problem is that breast cancer is indeed a systemic disease, and in the long run, if you follow these patients long enough, only about 25 percent remain indefinitely free of disease. Eight percent die each year, ad infinitum, even up to 20-30 years—between 20 and 25 years. 8 percent of the survivors will die. There is a little tendency to——

Senator KENNEDY. Well, of breast cancer or something else?

Dr. CRILE. Of breast cancer, yes—of breast cancer. Eight percent would die of breast cancer in each of these years, as long as you follow them. It is a little faster in the very beginning and it is a little slower at the very end—but not much. It averages out to 8 percent.

So our real problem is not local. We have so many means of controlling the tumor locally. The local recurrence is not a major problem today. Remember that the Halsted radical mastectomy was developed in England 110-years ago. It was popularized by Halsted 75-years ago. If you read the first 50 patients—the description of them in *Annals of Surgery*—of Halsted's first 50 patients, the average size of a tumor was described as being the size of an orange. Twenty-five percent of them had broken down and the cancers had ulcerated. There were matted lymph nodes, palpable—all of the things which now we would call inoperable. All of his patients were inoperable. At that time there was no radiotherapy, there was no chemotherapy—there was nothing except surgery to get rid of the great ulcerating mass.

Therefore, it was a good operation in its day. But now our problem is quite the opposite. We come in and find a woman who has a routine mammagram that shows some typical little calcifications—

you can't feel them or see them. A biopsy shows this to be a cancer. It seems to me the height of absurdity and ritualism to then perform a radical mastectomy.

The other thing is that the radical mastectomy is the operation that women fear the most. They fear its disfigurement, they fear its deformity, the lymphodema of the arm, a great deal of discomfort.

I have many times asked audiences, middle aged women, whether or not they had had a friend or a member of the family who had had a radical mastectomy. The prevalence of this disease is such that practically every hand in the room goes up—they have all known somebody who had it. You ask them then have they seen the body of that woman—and, again, more than half of the hands will go up.

Women who have seen this, this disfigurement, cannot bear to think of it happening to themselves. That is why I think that women should be widely encouraged by the media and everything else to seek early diagnosis, so that you do not have to do radical operations, and when women understand this, I believe that they will follow the advice of the American Cancer Society, perform self-examinations and have periodic mammagrams in women who are beyond the menopause, where it is of the greatest help.

Senator KENNEDY. You think that is a first order of priority?

Dr. CRILE. The first order of priority is to rid the American people of their fear of the treatment of breast cancer, because when you have breast cancers which are less than a centimeter in diameter, or those that are picked up only mammagram and are not palpable—you have a totally different incidence of lymph node involvement down to some 20 percent, and, to date, in the few studies that have gone on—the one from New York is the notable one—there has been about almost 50-percent reduction in mortality rate in the patients who were screened and had their tumors therefore discovered early.

And I think that that can be greatly improved as we get better methods of detection, which I think are inevitably going to come.

Senator KENNEDY. But preventive health care in this instance is just absolutely essential.

Dr. CRILE. The which?

Senator KENNEDY. The preventive health care.

Dr. CRILE. That is the only possibility of improving the survival, because no matter what you do locally, you cannot get rid of the systemic spread, unless our chemotherapy—which is very hopeful—and I am sure that you recognize, Senator Kennedy, that this has been the greatest single advance in leukemia, in childhood types of cancers and in osteogenic sarcoma. The patients with osteogenic sarcoma are now plateauing on a level 10 times the survival rate that they had before chemotherapy was used at the time of surgery. And this is most hopeful in every way.

Senator KENNEDY. Well, doctor, the point that you are making here is that many women have such fear of the disease itself, they are reluctant to come in in terms of preventive care—has that been part of your experience?

Dr. CRILE. Exactly. If we could get rid of the fear——

Senator KENNEDY. Fear of the treatment.

Dr. CRILE. If women did not associate the diagnosis of breast cancer with the deformity of a radical mastectomy we would then have women

who are much more interested in examining themselves or going for detection. And this has been my theme—and I think that the press and the TV people are and have been doing a magnificent job of making women aware of the fact that there is more than one way of treating a breast cancer.

Now, the argument that goes on is eternal between advocates of different types of treatment. I, by the way, am not an advocate of any type of treatment—I am an advocate of all types of treatment except the conventional Halsted radical mastectomy. Anything less than that, I think, has its place.

But the commonest operation that we do is the modified radical mastectomy, which is not a deforming operation and which is excellent.

Senator KENNEDY. You don't think there are any circumstances when the radical Halsted is—

Dr. CRILE. No; because, you see, if you have a tumor which is invading muscle and has gone that far, it is also totally incurable. If it involves 15, 20 lymph nodes, it is totally incurable by surgery—you have to rely on radiation. And radiation today, good radiation, deals just as effectively with tumor and lymph nodes as radical surgery does.

And there is much less local recurrence than—

Senator KENNEDY. You think there is sufficient scientific information to justify that?

Dr. CRILE. Sufficient what?

Senator KENNEDY. Scientific data and information to justify that—

Dr. CRILE. Oh, yes, you see, all of this has been worked out in many, many randomized tests abroad—that's exactly what I was coming to. In the randomized tests which have been done abroad for a number of years—there must be a dozen of them by now—and in no case has radical mastectomy been shown to have any advantage over simple removal of either the tumor or the breast with radiation—except in one test in advanced cancers, there seemed to be a little bit in the early years and that is rapidly changing as time goes on.

But there is no evidence that at least in stage I breast cancer, when you have no apparent involvement of nodes, that there is any advantage at all in doing a radical operation.

Senator SCHWEIKER. You are saying that in none of the overseas tests that are—

Dr. CRILE. None, in none of the tests has there been shown any advantage of any one form of treatment over another. Now, the trouble in things that mixes us up is, is that in this country we get anecdotal—and if we look at our Cleveland Clinic experience, for example, we would find two things, that is, that we would have a much higher survival rate today in the patients who were treated by a partial mastectomy, because those are the ones with small tumors and no involvement of nodes that are selected for that operation. We would find that the ones that were treated by simple mastectomy and radiation had the lowest survival, because we select for that, patients who have basically incurable disease. We would find a good survival amongst the modified radicals, but that doesn't mean that one operation is better than the other, nor does it mean, because one surgeon

reports from his experience that in his selection of cases that were treated by certain ways, that his patients had a 65-percent 10-year survival rate. That doesn't mean that that 10-year survival rate would apply across the board, if he were putting into it the same type of persons that other people do.

Now, without doing any radical mastectomies at the Cleveland Clinic, because we have only done less than 1 percent for the last 20 years—and none for the last 10 years—but doing none, basically, our 10-year survival rate is identical to the 10-year survival rate of the people in Fisher's trial who routinely did radical mastectomies during the same period—all of them had it—and of the cancer registry that Dr. Rauscher was speaking about just now in which they also had the 45-percent 10-year survival rate. Everybody has the 45-percent 10-year survival rate no matter how it is treated.

Senator KENNEDY. There are a number of authorities that will take strong issue with you, Dr. Crile, you understand that, don't you?

Dr. CRILE. They cannot take any issue at all with the randomized trials that I quote. Now, the anecdotal reporting, yes, I am sure, for example, that Dr. Haagensen, who I believe is going to testify here, will report a very high survival rate after 10 years for his treatment of breast cancer.

But you must remember that Dr. Haagensen has been the great pioneer in selecting the patients for breast cancer [sic] prior to his admonitions to the medical profession.

Senator KENNEDY. Well, I am not so much thinking of the doctor who will be here, but we have seen in the country perhaps two of the most prominent women who had access to the best in terms of medical information and advice—the first lady, Mrs. Ford, and Mrs. Rockefeller.

Dr. CRILE. Yes; but if I am not misinformed, Mrs. Rockefeller, who was operated on in New York, had a modified radical on one side and a simple on the other, not even an axillary dissection.

Senator KENNEDY. Well, you have Mrs. Ford.

Dr. CRILE. Mrs. Ford I know nothing about. There is no question at all that the incidence of use of the radical mastectomy is way down—for the first time. In a report that came out from Pennsylvania in 1974—this was sent to all hospitals in Pennsylvania—how many of each type of operation are you doing for breast cancer—and fewer than half were radical, for the first time.

By now I am sure that radical wouldn't be more than a third of the operations done for breast cancer in this country. It's on its way out.

Senator KENNEDY. I want to thank you very much for your testimony.

Dr. CRILE. Thank you, Senator.

Senator KENNEDY. And particularly your responsiveness in picking up the points we were talking about. Let me ask—what is your assessment of the amount of information that is generally available to women now in the country? What can you tell us about that in terms of the alternatives which are available to them? Do you think they are getting good information or not, as a physician?

Dr. CRILE. Well, I don't mean to be running an ad, but I wrote a book on this subject that is available in paperback. The title is "What Women Should Know About the Breast Cancer Controversy."

Senator KENNEDY. But what is your impression about the amount of information that is getting out to the women?

Dr. CRILE. I think it is there, if they can find it—the libraries all have information.

Senator KENNEDY. That's right, but I mean—

Dr. CRILE. Rose Kushner's book is out.

Senator KENNEDY. Sure. I am not questioning that there isn't information that's available, if they pursue it. But do you think that the average woman that is faced with this and goes to the average family physician in the average city, gets good information?

Dr. CRILE. You know, there are several things against change. One is economy—we spoke of that before—the radical mastectomy pays so much more than the simpler operations. There is no incentive for a doctor to leave it, no financial incentive.

When you are skilled—function lust, Conrad Lorenz calls it—you are a skier and, you know, it feels good to do a thing that you do skillfully, and in the same way a surgeon who has developed a certain technique, he likes to do that; it's hard for him to change. He needs some real prodding—and it is the kind of a prodding that comes from one of these studies, is the only thing that will make the doctor change. And the other thing that will make him change is, as was mentioned before, that women themselves demand the change. And the more women know about this subject, the more they are going to opt against the conventional radical mastectomy.

Senator KENNEDY. How well informed are the women now?

Dr. CRILE. I think pretty well. There was an awful lot on TV—they know there is a debate. They don't accept—they don't even accept a biopsy any more necessarily without staging it.

Senator SCHWEIKER. Doctor, what is the difference between the conventional radical and the modified radical mastectomy?

Dr. CRILE. The muscles are left. The conventional radical takes all of the muscles. The Halsted type has an incision that goes up over the shoulder—it was invented by the Devil himself, from the standpoint of cosmetics, because you can't possibly hide it. Most modified radicals go under the hairline of the armpit and remove the breast, but with a bra on and false in you really can't tell that anything is gone. These women look just fine.

Senator SCHWEIKER. Well, is your argument in terms of taking the simple as opposed to the modified radical, or—

Dr. CRILE. The modified radical, in my opinion, is the best all-around everyday use—if you have to settle for one operation, that would be the one to settle for.

Senator SCHWEIKER. What about the modified radical compared to the simple?

Dr. CRILE. I prefer the modified radical, because then you know what is in the axilla. I used to have a haunting feeling that the axillary nodes were part of the immune mechanism and should be spared. But the trials have not indicated that this is anything significant,

except for the fact that in every trial with radiation there has been a little bit more rapid death than in the ones that were not radiated. There were about seven such trials that were reported in *Lancet* about a year ago.

But anyway, in respect to—I lost my thread.

Senator SCHWEIKER. Well, we heard testimony earlier indicating that in all three options that there wasn't any difference so far in their study—now, they haven't finished last year—between the simple and——

Dr. CRILE. Well, the simple I don't like because you don't know what is in the axilla. And in order to know whether or not you should be given chemotherapy, which now becomes extremely important, you have to know what is in the axilla, whether the nodes are involved or not, because the chemotherapy would, at least so far—maybe it will become so that we give it to everybody with breast cancer whether the nodes are involved or not—but so far, at least, we have not used it except in women who have nodes involved.

So I believe it is important to dissect the axilla so that we can find out whether the nodes are involved—not a radical, complete dissection, but removing a good sample of the low and central axilla.

Senator KENNEDY. Thank you very much, Doctor. Very interesting and very informative.

[The prepared statement of Dr. Crile follows:]

Abstract

ADVANTAGES OF SIMPLIFIED TREATMENT OF BREAST CARCINOMA

George Crile, Jr., M.D.

It is well established by randomized clinical experiments abroad that the conventional radical mastectomy has no advantage over the modified radical mastectomy, and it has also been established that the supraradical mastectomy has no advantage over simple mastectomy and irradiation. The situation can be summarized by saying that if lymph nodes are involved it appears to make little difference whether they are removed surgically or irradiated.

Experience at the Cleveland Clinic indicates that if lymph nodes are involved it makes no difference whether they are removed prophylactically before they become palpable or, if after the primary tumor is removed, the nodes are allowed to remain until they become palpable and are then removed. For this reason, simple mastectomy, even when nodes are involved, is as effective as radical mastectomy provided the patient is followed and the nodes are removed if and when they become palpably involved.

There is suggestive evidence, both in the literature and in the Cleveland Clinic studies, that points to an advantage from the standpoint of survival when patients with no metastasis in axillary nodes are treated by simple mastectomy as compared to a comparable group treated by radical mastectomy. Moreover, in a series of more than 60 patients who have now been followed more than 5 years following local excision of small peripherally placed breast cancers, we have obtained results that from the standpoint of "5-year cure" and of incidence of local recurrence are comparable to those obtained in patients with similar lesions treated by mastectomy. In short, there is no evidence that the most radical operations, even when irradiation is added, are any more effective than simple operations that completely excise the local tumor.

Crile - 2

Since there is a vast increase in the amount of morbidity inflicted upon the patient when radical operations and irradiation are used, serious consideration must be given to methods of simplifying the treatment of patients with breast cancer and at the same time of maintaining a rate of survival that is comparable to that following more radical procedures. Evidence will be presented suggesting that in the early stages of cancers, removal or radiation of lymph nodes decreases the systemic resistance to reimplantation of the tumor and increases the incidence of metastasis.

The results of the National Surgical Adjuvant Breast Project indicate that when axillary nodes are involved the incidence of recurrence of cancer is greatly reduced if the patients are given L.P.A.M, a form of chemical treatment. In February, 1976, Dr. Gianni Bonadonna reported in the New England Journal of Medicine the results of his randomized trial of treating patients with nodal involvement with 3 chemical agents (C.M.F.). After 27 months there had been only 5.3% recurrences of cancer in the treated patients compared with 24% of the untreated controls.

The New England Journal editorialized on the spectacular early success of this treatment and queried "Can the extent of radical surgery be decreased?" It is hoped that it can, for the fear of radical surgery or even of routine loss of all the breast is the main reason why women do not examine themselves periodically, do not insist on having occasional mammograms, and delay reporting to the physician the finding of a lump.

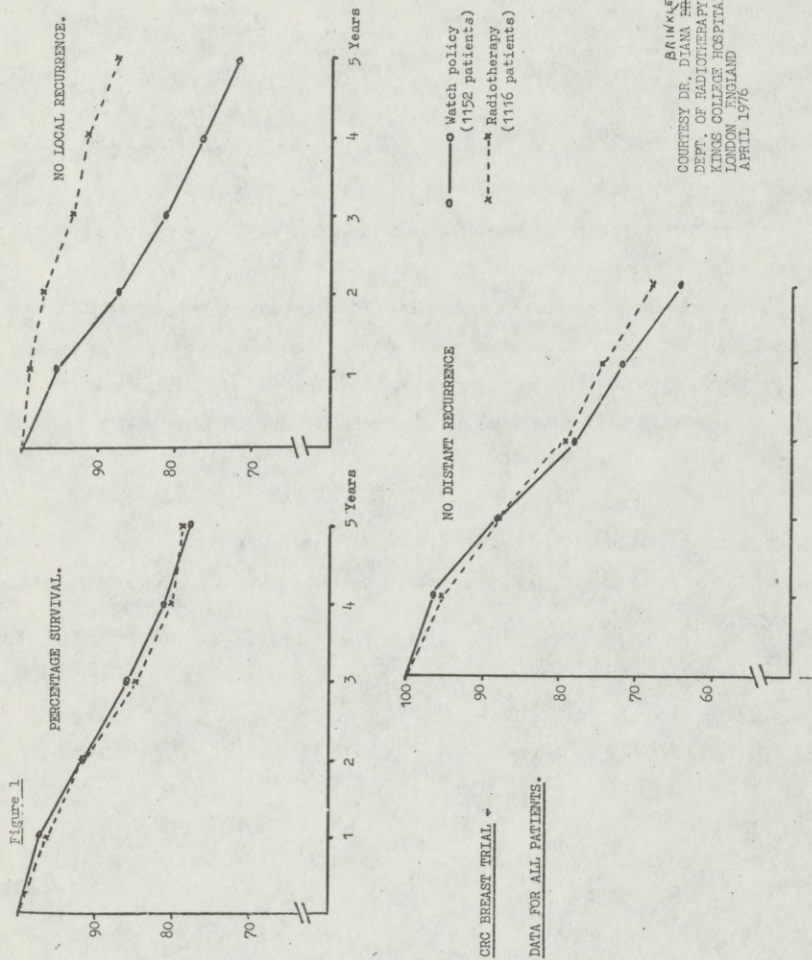
Already it appears as if this hope has come true because in February 1976 the National Cancer Institute approved a prospective randomized trial to be conducted by Dr. Bernard Fisher and his National Surgical Adjuvant Breast Project to compare the results of modified radical mastectomy in Stage I breast cancer with partial mastectomy and axillary dissection and with partial mastectomy, axillary dissection

Crile - 3

and radiation. The National Cancer Institute would not have approved this study had there been any proven difference in survival.

Finally the 5-year results of the Cancer Research Trial in England are now available. This was a randomized study between simple mastectomy and simple mastectomy and radiation and involved 2368 patients. In the group assigned to simple mastectomy alone, no treatment of the nodes was permitted for four months, even when the nodes were obviously involved. At 5 years there was no significant difference in the proportion of survivors. Local recurrence was higher in the non-irradiated group, but this was usually controlled by surgery or irradiation with the result that after secondary treatment there was no significant difference in the two groups in the proportions of patients with persistent local recurrences. (See graphs Figure 1)

A result such as this paves the way for reductions in the extent of surgery and in the amount of mutilation and disability that in the past has been needlessly inflicted. It is only through such studies that the results of treatments can be evaluated and that progress can be made both in the cure of cancer and in the reduction of the morbidity inflicted by treatment.



Senator KENNEDY. Our final witness is Dr. Cushman Haagensen. Dr. Haagensen is emeritus professor of clinical surgery at the College of Physicians and Surgeons of Columbia University. He is accompanied this morning by Dr. Darrow Haagensen, research assistant, Department of Surgery, Duke University, and Dr. Sven Kister, associate clinical professor of surgery at Columbia University.

Would they be kind enough to come up? Doctor, we welcome you here and look forward to your testimony. I understand you have some slides. We have your testimony and we can include that in the record as if given—and then you can either summarize it or highlight it, or whatever way you want to proceed.

STATEMENT OF CUSHMAN D. HAAGENSEN, M.D., EMERITUS PROFESSOR OF CLINICAL SURGERY, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY; ACCOMPANIED BY DARROW HAAGENSEN, M.D., Ph. D., DEPARTMENT OF SURGERY, DUKE UNIVERSITY; AND SVEN KISTER, M.D., ASSOCIATE CLINICAL PROFESSOR OF SURGERY, COLUMBIA UNIVERSITY

Dr. CUSHMAN HAAGENSEN. Thank you, Senator Kennedy, for the opportunity to speak to your subcommittee.

You know very well that my opinions as to treatment of breast carcinoma—indeed also as to its diagnosis are quite different from those of Dr. Crile and also Dr. Fisher.

I beg of you to consider, as I present my evidence, that our differences of opinion don't depend upon any difference in good will. They depend upon experience. Experience is the thing that conditions us all in life. And I shan't say anything about their experience, but, I might mention my own. I have been concentrating upon diseases of the breast for more than 40 years at Columbia. And during this period of time I have had an unusual opportunity to work with patients, as I needed them, to have very expert pathology—I am a pathologist myself as well as a surgeon—and to have an unequaled followup of our patients.

Followup is one of the essential things in the assessment of treatment in many diseases. And all of my life, until very recently, Senator, the followup in our hospital has been of a rather special kind. It has been carried out by the attending surgeons themselves, not by the interns and residents. Women who have serious disease won't keep on coming back if they see a different young physician every time, but if they know the attending physician who took care of them, and they become friends with him, they will come back almost indefinitely. Very recently in our hospital, a new hazard has appeared to our followup. It is that formerly it was free—now, in our hospital, the administration collects \$27 for every patient who comes to followup. The result is that the patients won't come back.

This is an aspect of our problems of collecting data, which is so vital in our studies.

Senator KENNEDY. Let me just ask you, Is this in the clinic?

Dr. CUSHMAN HAAGENSEN. This is in the clinic. And more than half of my patients have been clinic patients.

Senator KENNEDY. I see, but that used to be free?

Dr. CUSHMAN HAAGENSEN. Followup visits have until recently been free in our clinic. When our institution was set up, it was realized by the full-time men who set up our system that very complete clinical records, very complete pathology, and a very complete followup were essential steps in reaching any decisions about modern disease.

I cannot overemphasize the necessity of followup—and of personal followup.

Senator KENNEDY. Did you find much abuse of free followup consultations?

Dr. CUSHMAN HAAGENSEN. Oh, no, women with serious disease don't abuse followup.

Senator KENNEDY. Well, that is my impression, but I have listened to distinguished people sit in that same seat and give quite a contrary opinion that don't have nearly the experience that you have.

Dr. CUSHMAN HAAGENSEN. My experience is that women who have serious disease are incomparably courageous, for one thing. They will come back and help in every way in their treatment. And they don't abuse it.

Senator KENNEDY. Not today, but I would be interested in how you offered the free service—and now you charge \$27. I don't want to take up your time—and that is not the subject of this particular hearing—but if you could have one of your people give us a brief note on it.

Dr. CUSHMAN HAAGENSEN. I have never been an administrator, Senator. I have been always someone who worked with disease. So I don't know myself how our administration reached their decision to charge for followup.

Senator KENNEDY. Well, just later on, not now. Let's get on with the other.

Dr. CUSHMAN HAAGENSEN. Now, may I continue a moment about my experience. I have been through these 40 years—spent thousands of hours myself examining patients. And I have examined almost all the consecutive carcinomas that came to our clinic myself although occasionally it has been done by my associates like Dr. Kister. I also am deeply concerned with the pathology, and I usually see the pathology myself. I do the followup myself very often. I am therefore continually engaged in correlating the findings at followup with the findings at our initial clinical examination. This is how we learn—from personal experience intensively carried on over a long period of time. And I shan't mention the thousands of hours I have spent in the operating room, operating on these women.

So that I have had a kind of experience which you may compare with that of other people who have testified before you.

Now, I know that the main direction of your interest today is how best to treat breast cancer—and indeed this concerns us all. It is our basic interest.

Now, in order to approach that question properly, I would like to show you a few lantern slides. And could we begin with one which shows diagrammatically what I might call the natural history of breast cancer?

The important point to realize is that it is a very slowly progressive disease and its progress depends primarily on the feature shown in the

central column in my slide, under "Pathology," that is, the doubling time. By this I mean the time it takes for the original cancer cell and successive cancer cells to double in number. There have been a number of studies of doubling time, and in general it is agreed that the doubling time is, say, 2 or 3 months.

Now, from the first cancer cell which arises—we don't know why—by mutation from a normal cell, 30 doublings are necessary, requiring 4 or 5 years, to produce a breast tumor 1 centimeter in diameter, which you can easily feel. So that the process is a very slow one. We know that it is 4 or 5 years, because, of course, we know the diameter of a single cell and you can calculate the increase in diameter over 30 doublings.

The tumor then becomes palpable—and it is perhaps detected by palpation. Of all the methods of detecting breast disease, including cancer, palpation is the simplest, most practical and most accurate.

Some time during this progression, the disease breaks loose and metastasizes to the axillary nodes. The axillary nodes are a wonderful filter to catch and protect the body against disease.

The next step is that the disease progresses in the axilla until the axillary nodes become palpable. This second step, as I have shown in my diagram, takes 1 or 2 more years. Now we have got up to, say, 5 or 7 years. And the next, third, step is that the disease becomes extensive in the axilla and it begins to spread beyond the axilla to the internal mammary nodes. The primary tumor in the breast meanwhile grows—and a variety of signs of the increasing extent of the disease in the breast become apparent clinically. I have listed some of them here—skin edema, ulceration, satellite skin nodules, and so on.

If there is no treatment, this third stage requires 2 or 3 more years to death.

But if we now turn to the possibilities of treatment in the righthand column, you can see that it is extraordinarily important—indeed basic—that we estimate as best we can from clinical signs the stage of advancement of the disease, because accurate determination of the stage of advancement is the key to the selection of treatment.

We now have at least two reasonably accurate methods of clinically classifying the extent of the disease in the individual patient. One is the so-called international classification developed by the International Union Against Cancer. The other is our Columbia clinical classification, which we devised some 20 years ago, and has been adopted in a fair number of clinics.

And on the basis of our Columbia clinical classification, we divide the disease into stage A, stage B, and stages C and D. I will discuss these stages later on.

But I must tell you that from long years of experience, operating upon patients in these four different clinical stages, we have come to realize that operation—and our operation is radical mastectomy—should be done only in clinical stages A and B, and that in stages C and D, no operation really does much good—the disease is now incurable. It's incurable by surgery, radiation, chemotherapy and every method we know about. These methods prolong life, of course. But it is incurable in the sense of my working definition of cure, which is survival for 10 years. You have to make a point somewhere in your

followup at which you decide there is a reasonably good chance that the patient is cured—and this is at 10 years, because, although recurrence does sometimes occur after 10 years, it is infrequent. After 10 years the curve showing normal loss of life in women who do not have breast cancer is parallel with the loss of life in the patients who have been treated for breast cancer.

Senator KENNEDY. Doctor, wait a minute, before we leave this one here.

Dr. CUSHMAN HAAGENSEN. Yes.

Senator KENNEDY. I think what we have to ask, though, is whether those figures on the right side—that 67-percent, 10-year survival and 38-percent, 10-year survival—would have been any different with the more modified mastectomy.

Dr. CUSHMAN HAAGENSEN. I have got this all coming up, if you will permit me.

Senator KENNEDY. Fine.

Dr. CUSHMAN HAAGENSEN. I have got precise tables which show these comparisons of different methods of treatment.

Senator KENNEDY. Fine.

Dr. CUSHMAN HAAGENSEN. This is just an introduction. Now, here is our Columbia clinical classification. Its great advantage is that it is simple—you can remember it. It's practical. The international classification is so complex that you can't remember it, and therefore it isn't very useful.

Next slide, please.

A friend of ours, Richard Handley, currently president of the Royal College of Surgeons, who advocates our Columbia classification, has compared the Columbia classification and the international classification in his series of cases. At the left is the Columbia classification, at the right is the international classification.

You will see that Handley gets a better spread of survival rates with the Columbia classification than he does with the international classification. And these differences are very important in terms of accuracy for us.

Next slide, please.

The Columbia classification, with us and in a number of other clinics, has been a practical way of determining the extent of the disease in the individual patient. I have heard some of your people testify today that this is impossible to do. Not so. We can do it with really a high degree of accuracy.

Now, the next stage of advancement of breast cancer, which is disastrous to the patient in a general sense, is the spread of the disease into this wonderful lymph node filter in the axilla. This diagram shows this filter. There are about 30 axillary nodes—which we dissect out of the axilla when we operate. We count the number of nodes that contain metastases very carefully. These figures are of great importance. I will show them to you later on.

Next slide, please.

Now, here is an example of an early onetastosis in an axillary node, three little groups of cancer cells which have spread to a node in the axilla. This is the phenomenon which so often defeats us.

Next slide, please.

Now, I should like to show a chart, if I may, Senator, from my own series of radical mastectomies, all followed for a minimum of 10 years. I now have about 1,000 such cases. The 10-year period has not been reached in all of them, but this slide shows the 10-year results in 882.

I should like to point out that in clinical stage A, there were 418 patients who at operation proved not to have any axillary metastases. In them the 10-year survival rate was 76.5 percent.

But there were 131 patients in whom one to three nodes contained metastases. With the operation which we do, the radical mastectomy, in which we carefully remove all the nodes in the axilla, as we did in these patients, our 10-year survival rate in these patients who had one to three nodes involved in the axilla was 68 percent.

In stage B the results are not so good, of course. But let us think now more about these early stage A cases. In Dr. Fisher's protocol for his experiment with random choice of treatment, one choice is not to treat the axilla at all. In these women in whom he does not treat the axilla, we know that a considerable proportion will have metastases in the axilla. And if the axilla is not treated, the patient will succumb to the disease. This is human experimentation in the situation where the pathological facts are well known.

Do you have any questions at this point, Senator Kennedy?

Senator KENNEDY. No—well, the only point I am making, we are not the judges up here of—

Dr. CUSHMAN HAAGENSEN. These facts are rather simple.

Senator KENNEDY. Well, they may be very simple, I am sure they are to you, but they are not so clear and convincing and persuasive to the head of the Cancer Institute as it might appear to you.

And we are generalists—we have a responsibility to try to find ways and means of looking after the health—and we are not going to make a decision at the end of this meeting that you are right and Dr. Crile is wrong or Dr. Rauscher is wrong or whatever—I mean, we can be helpful to you in getting your best information to the Cancer Institute and to make sure that this is given.

But what we are attempting to do is interpret for the lay persons, the women of this disease, where their best interests lie. And I know that you want to make your case in terms of the persuasiveness of your own position. That is why we have you here today, because we understand you have a strong view on the other side of what has been proposed to you. And so we want to hear you and we want you to do it in whatever way you think is best suitable.

But, you know, you are talking, just by the nature of this hearing, to generalists on these particular parts—and I think these are helpful and useful in terms of our record and our documentation on it, but I am sure you understand that if we had experts up here, they would be cross-examining you and taking rather serious issue, I suppose, with a number of these various points.

Dr. CUSHMAN HAAGENSEN. Senator Kennedy, an opinion unsupported by scientific facts means nothing. I am trying to give you some scientific facts. If you don't have time for them, then I am sorry.

I can perfectly understand why they might—

Senator KENNEDY. No; we have time for them—and I think it is useful in terms of the supporting of your position.

Dr. CUSHMAN HAAGENSEN. You must forgive me, Senator Kennedy, for presenting my facts with some emphasis.

When a woman comes to me with a breast cancer—

Senator KENNEDY. But let's continue, if you would like to briefly go through, and then we can come back to the broad policy questions which I think are the kinds of things that we are going to have to basically deal with.

Dr. CUSHMAN HAAGENSEN. Yes; I say I can't restrain myself from presenting facts and presenting them with some emphasis. I apologize if the emphasis disturbs you.

May I go on with some of the facts?

Senator KENNEDY. Fine.

Dr. CUSHMAN HAAGENSEN. All right, let's skip along. Now, we have data concerning predisposition of women to breast cancer. There are several groups of women who are heavily predisposed—and these facts are not known to Dr. Rauscher, at least in 6 and 7—particularly 7—but I won't pause to describe them further.

If you know the women who are going to get breast cancer, you can follow them much more carefully—and, therefore, perhaps detect their disease at an earlier stage.

Senator KENNEDY. Please proceed.

Dr. CUSHMAN HAAGENSEN. Again, I must state the facts. In any comparison of the results of the different methods of treatment, there have to be rules which are followed; otherwise, comparison means nothing.

And our results, which I will present to you in a moment, have been compiled on the basis of these rules. First of all, the unit case records, which are the basis of all scientific data in our hospitals, must be very complete. Second, the clinical stage of advancement of the disease must be accurately classified by one of these clinical classifications; otherwise, you cannot know at what stage your patient's disease happens to be. And in comparing the results of treatment, you have to compare the results of one method of treatment in one stage, say, stage A, with the results of another method of treatment also in stage A. In other words, you compare the results stage by stage.

Do I make myself clear?

Senator KENNEDY. Yes.

Dr. CUSHMAN HAAGENSEN. This clinical classification is basic. Now, I must say that in Dr. Fisher's protocol for his joint study, there is no clinical classification of this kind, in terms of the two recognized clinical classifications. And without this kind of clinical classification it is going to be impossible to compare the results of the different methods.

Third, the case histories should consist of consecutive patients, because if you start omitting patients, at once you get into trouble because you are very apt to omit the advanced ones, and so forth.

Fourth, the technique of treatment being tested must be fully described and carefully followed. In my series of a thousand radical mastectomies, all of the operations have been done with the same technique, with myself or one of my associates always there disciplining and watching the operation. There has been no variation.

Fifth, only patients with generally accepted types of breast cancer must be included in these studies.

One special type of disease which is not truly cancer, is sometimes included, because it is commonly called lobular carcinoma in situ.

Finally, the results should be expressed in terms of the numerical frequency of local recurrence, as well as survival at 10 years. And in these studies, of course, patients dying of recurrent disease or lost track of, are all counted as dying of cancer.

Now, so much for the rules that we have followed and that we believe are necessary to make comparisons.

Next slide, please.

Here are the 10-year results in my consecutive series of patients, treated by radical mastectomy. There are included here 194 patients who, as a matter of fact, did not have radical mastectomy because we had a biopsy method of proving that their disease was incurable by operation. Nevertheless, since in other clinics these biopsy methods aren't used, so that these patients would have been operated upon in other clinics, we have included them in our report. Here are the results in all our 1,076 patients, by clinical stage.

Next slide, please.

Now, of the different methods of treatment currently used—a common one, which Dr. Crile has used very extensively, is local excision of the palpable breast tumor, or lumpectomy, followed by radiation. There is only one clinic from which the end results of this method of treatment have been carefully presented, and this is from Dr. Peters in Toronto. And she has presented her results only for clinical stage I of the international classification. She has 129 patients. Her 10-year survival rate is 44.5 percent.

When you take my total number of patients in stage I treated by radical mastectomy, my 10-year survival rate with radical mastectomy is 73 percent.

So much for lumpectomy.

Dr. Crile has repeatedly advocated lumpectomy on NBC in New York, and many women have now had it because of his advocacy of it. It seems to me that these are facts which should be considered in the choice of treatment.

When I deal with women who come to me asking how they are to be treated, I show them these facts. And I am glad to have any one challenge them. I think they are so simple, Senator, that any one can understand them.

Next slide, please. Now we come to Miller. Miller is a remarkable man in Detroit who has a series of patients treated by simple mastectomy only. It is the best series, I believe, in the sense that the operation was carefully done—all the patients are followed. And he uses the Columbia clinical classification. In stage A his end results for simple mastectomy are 40 percent, and in stage B 26 percent.

Now, in our comparative series of patients treated by radical mastectomy they are 67 percent and 38 percent.

So much for simple mastectomy alone, which I remind you is one of the random alternatives of treatment which Dr. Fisher uses in his patients.

Next slide, please.

We come next to the method of treatment which is more widely used in the modern world than any other one. It is McWhirter's method. McWhirter is a Scottish radiotherapist, who about 25 years ago began advocating simple mastectomy followed by radiation. And this is more widely used than any other method in the British Isles and is often used in this country also. It is widely used in Europe.

Here are Dr. McWhirter's latest results compared with our own for stages I, II, and III in the international classification. McWhirter's 10-year results are 54, 43, and 24 percent. These data are very simple; his statistics are very well put together. Our 10-year results in our own series of radical mastectomies, consecutive patients, classified by the same method are 76, 52, and 40 percent.

Again, it seems to me that these figures are——

Senator KENNEDY. I was just asking counsel on the earlier treatment—I guess it was the Peters study—did that have any chemotherapy in it?

Dr. CUSHMAN HAAGENSEN. No; none of these patients had chemotherapy.

Senator KENNEDY. So what you are really talking about is comparing just surgery without chemotherapy?

Dr. CUSHMAN HAAGENSEN. Yes, indeed.

Senator KENNEDY. I didn't understand that——

Dr. CUSHMAN HAAGENSEN. Oh, I am sorry.

Senator KENNEDY. I think it is important, again, that you define your terms, because I don't know anyone that believes that they ought to do just the surgery without chemotherapy.

Dr. CUSHMAN HAAGENSEN. May I ask Dr. Kister——

Well, may I say one word—and I hope that you will ask Dr. Kister some of these things, because——

Senator KENNEDY. Well, I am not going to ask too much, because it is not really up to me. But I have been looking at figures which show yours versus others, and we find out that the others is not even something that is normally being considered to be a legitimate——

Dr. CUSHMAN HAAGENSEN. May I say, Senator Kennedy, I don't know anyone who has reached 10 years in chemotherapy.

Senator KENNEDY. That isn't what the question was.

Dr. CUSHMAN HAAGENSEN. Yes; that is why it wasn't used in these patients. We are aiming for cure, 10-year survival.

Dr. DARROW HAAGENSEN. Senator Kennedy?

Senator KENNEDY. Yes.

Dr. DARROW HAAGENSEN. You just heard testimony this morning on one of the studies where three types of surgery were tried without any adjuvant therapy—1,700 patients. They testified this morning that the three types of surgery gave no difference.

Now, then, of course, current studies are adding chemotherapy, for which we have data from some of our studies.

But the point is, Fisher's original study is exactly this data—simple versus modified versus radical—without any chemotherapy. So you have heard it. He states there is no difference.

Senator KENNEDY. Is that the modified one that Dr. Rauscher was talking about which they testified to as being virtually without substantial difference?

Dr. DARROW HAAGENSEN. Yes; it is—I mean, it is right there in front of you, 1,700 patients, there is no chemotherapy given on those—4 years.

Dr. CUSHMAN HAAGENSEN. Chemotherapy is something comparatively new.

Dr. KISTER. Senator Kennedy, if I may.

Senator KENNEDY. Yes.

Dr. KISTER. It is precisely the point that Dr. Haagensen is trying to make, that the conclusion to which Dr. Fisher came in his famous paper of 1971, which he declared that there is absolutely no difference to be found between the various methods of surgical treatment. What we are trying to point out is that there is.

Now, what you are going to do further, or whatever else—maybe surgery is not the answer at all to cancer, it probably isn't—is not the point here. But we are trying to tell you or present to you the facts that the starting lines in this race for cure are quite different. And maybe if one would add something to these data that in itself are better. Adjuvant chemotherapy—if it proves to be indeed a useful adjuvant, which I may address myself to you in a minute, if you will permit me—then I think there is a great deal of difference. We should probably not abandon methods that have proven to be superior, but we should add them until we reach 100 percent cure.

I think this is the point that Dr. Haagensen is really trying to make.

Dr. CUSHMAN HAAGENSEN. Well, anyway, here we are with the continued comparison of the different surgical methods of treatment.

Now, I show you last of all the results of my friend, Richard Handley, who does the best modified operation, I believe, anywhere. And he uses the Columbia clinical classification. His patients are all consecutive patients, and with his modified operation, 10-year survival rate in stage A is 60 percent and in stage B 32 percent, as compared with my radical mastectomy survival rates of 67 percent and 38 percent.

Now, would you show the next slide? I want to show only two more slides, which are, I think, important in this context of choice of treatment.

Here are two series of patients treated by radical mastectomy in whom local recurrence developed following mastectomy. And I want to point out that there are virtually no 10-year survivors after local recurrence, so that local recurrence is a very grave, indeed usually fatal, phenomenon.

Next slide, please.

Here are the 10-year local recurrence rates following four different methods of treatment for which I have presented 10-year survival rates. In clinical stage A, following Miller's simple mastectomy—37 percent local recurrence, following McWhirter's method, of simple mastectomy and irradiation done by the Danes Kaae and Johansen, 19 percent, and following Handley's method of modified mastectomy 12 percent. In our series of radical mastectomies, 6.5 percent.

In stage B the results aren't as good, but the differences still exist favoring radical mastectomy.

So that we can show you—and we have shown you here—that we get less local recurrence following our radical mastectomy than even after the modified operation, which is the closest one to our radical mastectomy.

I would like to finish by saying that breast cancer is a very dangerous and often fatal disease. I have shown you a surgical method which gives a realistically better 10-year survival rate than any other method. And I am not now talking about chemotherapy. Chemotherapy is something which has not yet proven its value. No patient has survived beyond a very short period of time with chemotherapy.

But even when I show you that the difference is only 6 or 7 percent between a modified operation and a radical operation, when I have done 1,000—and I have—I have saved or brought 60 or 70 women to the 10-year survival rate who would have not got there with the lesser operations. And I have to ask you, what is my duty in life? It is to give my patients the best possible treatment?

And that is why I stand on radical mastectomy as the preferable method of treatment today.

Now, these are facts. I have not given you any opinions, I have given you facts. And these are well-known to Dr. Fisher and to Dr. Rauscher and to Dr. Crile. We debate them endlessly—we never get anywhere in our debates.

Dr. KISTER. Senator Kennedy, if I may take the liberty to point to you what dilemma can arise from this kind of a confusion that presently exists, I would like to show you a slide which illustrates this.

As you well know—I am sure this was reported here many times this morning—the Bonadonna study from Italy and the CMF as an adjuvant treatment to all surgical patients that had any nodal involvement. Now, the surgical treatment in the Bonadonna group was classified as either radical mastectomy or extended radical mastectomy, as done by Dr. Veronese, and in this country as popularized by Dr. Urban. There are many other qualifying statements for the entry into this study, one of which particularly interested me. It said that there had to be geographic accessibility to a treatment center. We all know, for instance, that social status and economic status have a great deal to do with the disease behavior. This in itself could have modified the selection of patients a great deal.

But, certainly, the previous treatment is important. And indeed the differences in the one- to three-node category that were positive in their series were significant.

The first line on the curve shows—the “B” stands for Bonadonna and the CMF stands for cytoxan-methotrexate, fluorouracil, which is the triple combination given to the people in Italy. The middle line stands for my initials. And the lower line is the control of Bonnadonna’s.

These are redone figures. I have another slide showing another point of—what this is to bring out, the center group are not Dr. Haagensen’s patients, but I also had nearly 500 patients on whom the Haagensen’ radical mastectomy has been done—in the 1-3, positive lymph node group. And this leaves me wondering, since the results are so little different, certainly not statistically significant—and the follow-up period on Bonnadonna’s series is so awfully short, the 28-months figure on Bonnadonna’s scale represents, Senator Kennedy, an estimated five patients.

One wonders, am I morally justified to expose these people to these drugs, which are not innocuous. This question or this point of the danger or the effectiveness of chemotherapy is shared by many. And

I believe that Dr. Rauscher and Dr. Fisher have presented only one point.

And if I may just briefly tell you something about this. [Dr. Constanza] in a recent letter in the New England Journal of Medicine writes with a great deal of concern:

The pervasive air of imminent triumph has created an unfortunate situation in which rational evaluation of ongoing studies becomes impossible.

Both the Fisher study, where he added originally only L-PAM, as well as the Bonadonna study, qualify as such, because—and here again I have point-blank copied Bonadonna's study from the New England Journal, and my own—and you realize that we are dealing here with an average or mean follow [sic] of 14 months. The recurrence rates in Bonadonna's series, indeed in the untreated group, are much less than in ours.

There are several important points that should be made at this juncture, and I indeed hope and would wish that I knew how to achieve the 100-percent cure rate—hopefully with very little or no surgery. But we have this dilemma of knowing the following facts. To my knowledge, in an epithelial malignancy, what is otherwise known as a carcinoma—I am not talking right now about sarcomas or leukemias or lymphomas—nobody with established metastasis has ever been cured by chemotherapy. And that is an important intellectual consideration, because it indicates something—certainly we have all seen tremendous regressions in established metastasis and virtually disappearance of disease by all presently known methods for detection, but they eventually all recur.

Yet, sooner or later, 16, 18 months, the failure sets in.

Nor do we have long enough or adequate follow-up in any of the studies to show us that either life has been prolonged—we have only that the disease-free interval has been prolonged in a very short period of time, maybe 12 to 14 to 16 months, and the differences are very small. Are we already truly justified to take this preliminary data and expose, for instance, 68 percent of women who we know live to a ripe 10 years without disease, and expose them to CMF, which is known to have side effects, short term and long term.

I, for myself, cannot yet bring myself, nor can many of the oncologists come to this point of view, to add adjuvant chemotherapy to all patients. And this has created a problem which is almost intolerable to the patient as well as to the physician. In fact, it can observe a most useful form of treatment due to the premature conclusions drawn from these studies.

I have recently been in situations where a patient would ask me what I would do, and I will express my views, based on facts, and I advise her very sincerely to go around in New York or in Boston—the two eastern Medical Centers that I know of significance—to Dr. Kelly at the Massachusetts General, to Dr. Constanza at the New England Medical Center, people at Memorial, at Mount Sinai, Dr. Holland, will give the same patient diametrically opposed points of view. And this is really the consumer's dilemma. If we at these Centers can't make up our mind—what does one expect from a doctor who works in Hanover, N.H., or what is the patient to do, if she gets a 50-50 break for and against CMF for one to three nodes positive with data presented to you from our medical center?

This is truly a dilemma.

Senator KENNEDY. Could I ask Dr. Haagensen, did you do the radicals on all women, or did you have a certain criterion of operability?

Dr. CUSHMAN HAAGENSEN. I have selected my patients following strict criteria, as I tried to show you, Senator Kennedy. We do the radicals on patients whose disease is stage A and B only. And our classification is pretty accurate.

Thus we reserve our operations very carefully for the patients who we think have a reasonable chance of cure with the operation.

Senator KENNEDY. We will make sure to get this complete presentation sent out to Dr. Rauscher, and I am going to ask him to make a comment on it and come back to us.

Dr. CUSHMAN HAAGENSEN. He knows all about this. My data have been published long since. Indeed, it is in my book, *Diseases of the Breast*, which is known all over the world and available to everybody.

Senator KENNEDY. Well, that will be the best that we can do, we are not going to be able to resolve it. We hear the testimony through the Cancer Institute, talking about their trial to compare the results of radical mastectomy to those obtained following a lesser procedure—total (sometimes called simple) mastectomy, with and without post-operative radiation.

It has been emphasized that strict guidelines for patient acceptance and all the protocols be rigorously adhered to by August 1974. When patient accrual was terminated, almost 1,700 patients were entered into the evaluation, with the average followup time was 30 months. To date there is no significant differences in the results between the treatment groups.

All we can do is ask you to analyze either theirs and then we will ask them to analyze yours.

Dr. DARROW HAAGENSEN. Yes, Senator Kennedy. I think it is the philosophy of the study that is important, and maybe an analogy would help you clarify it—which is, if you were racing a Ford “Pinto” and a Volkswagen “Rabbit” and a Chevrolet, and you got to the end of the race line, none of them won—OK—you can do it 5 times, you can do it 10 times—but the next time you pull up a Ferrari, there is no question what’s going to happen.

The same philosophy goes in this surgery exactly. You are comparing three types of treatment by the average surgeon who does it in the morning, and an appendix in the afternoon, versus a surgeon who is doing it very carefully, taking three times the amount of time to do the operation, trying to get all of the cancer out.

The only way to cure cancer is to remove it 100 percent. Now, no one has been able to leave cancer in and cure it.

Dr. CUSHMAN HAAGENSEN. Senator Kennedy, I don’t look to you as Solomon. I don’t expect any decision. All I want to do is to present the facts, and I am grateful for the opportunity to present the facts. The facts are not very complex—and they represent the discipline, the medical, pathological, surgical discipline of the institution in which I have spent my life, Columbia Presbyterian Medical Center.

Thank you very much.

[Additional material supplied for the record follows:]

HARRISON A. WILLIAMS, JR., N.J., CHAIRMAN
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United States Senate

COMMITTEE ON
 LABOR AND PUBLIC WELFARE
 WASHINGTON, D.C. 20510

May 14, 1976

Frank Rauscher, Ph.D.
 Director, National Cancer Institute
 National Institutes of Health
 9000 Rockville Pike
 Building 31 Room 11 A 52
 Bethesda, Maryland 20014

Dear Dr. Rauscher:

Thank you very much for your appearance before the Health Subcommittee on May 4th to discuss progress in the treatment of breast cancer.

After your statement was completed, Dr. Cushman Haagenen of the Columbia University College of Physicians and Surgeons testified. He presented some data which appear to indicate that, at least in his hands, results of the classic Halstead radical mastectomy were considerably better than was indicated to be the case by the testimony delivered by you and Dr. Fisher.

I am enclosing a copy of Dr. Haagenen's statement, and would greatly appreciate your reaction to it.

Sincerely,

Edward M. Kennedy, Chairman
 Senate Health Subcommittee

cc: Dr. Cushman Haagenen



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND 20014

NATIONAL CANCER INSTITUTE

JUN 9 1976

The Honorable Edward M. Kennedy
Chairman, Subcommittee on Health
Committee on Labor and Public Welfare
United States Senate
Washington, D.C. 20510

Dear Mr. Chairman:

Thank you for your letter in regard to my testimony and that of
Dr. Cushman Haagensen of the Columbia University College of
Physicians and Surgeons. I have asked Dr. Vincent DeVita,
Director, Division of Cancer Treatment, to review Dr. Haagensen's
statement on breast cancer; his comments are enclosed.

Sincerely yours,

Frank J. Rauscher, Jr., Ph.D.
Director, National Cancer Program

Enclosure

Comments on Dr. Cushman Haagensen's Statement on Breast Carcinoma

Halsted described the radical mastectomy in 1894--82 years ago--based on principles of tumor biology we now know are outmoded. He felt that cancer spread directly only through lymph glands; the propensity for cancer to spread via the blood vessels was unknown at that time. We now know that even in the earliest stages of tumor growth tumor cells are shed from a tumor mass into the circulation as well as draining lymph glands. We strongly suspect the host's own defenses are able to control some of these circulating cells, in small numbers, accounting for cure when the primary tumor is removed, even after shedding has occurred. We no longer consider the lymph glands draining any tumor an impenetrable, or even an efficient, barrier.

For the commonest, most malignant forms of breast cancer, the following points are axiomatic. The larger the tumor, the more likely lymph glands are to be involved; the more lymph glands involved the worse the prognosis; when lymph nodes are involved, the ultimate problem leading to death is not local recurrence (cancer recurrent in the operative field) but distant metastases. Patients rarely, if ever, die of locally recurrent disease. Even when disease first appears locally, the great majority of patients have evidence of distant metastases coincident with identification of the local recurrences, or within three or four months after their discovery. Simply put, the attempt to prevent "local recurrence" has been a straw man for continued and more aggressive local attack of the primary tumor with radical surgical procedures and postoperative radiotherapy. The latter has been shown to have no effect on survival and sufficient morbidity to hasten its abandonment as a routine postoperative treatment, a step that is proceeding, if slowly.

The reason survival in breast cancer plateaued around the mid-50's was local therapy, however aggressive, controlled local disease and no more. This amounted to some 45% of the women with breast cancer, failure to cure the disease was due to distant, invisible, (by standard methods) metastases. Therefore, it might have been viewed as futile, long before it was, to explore increasingly radical methods for local control for a problem related to disease outside the operative or radiotherapy field, without considering an alternate hypothesis; that less radical procedures were as good, and, since they are less morbid, would be a better choice.

In my view, Halsted would be the last person today to accept the continued use of the radical mastectomy without question. He envisioned the procedure as a way of controlling very advanced large, bulky tumors of the breast. Dr. Haagensen's statement, regarding Halsted's success

-2-

in controlling local recurrences, in his first 50 cases, is true, but misleading, since both Drs. Haagenson and Halsted were referring to local recurrences only. Survival was actually very poor in that group of patients.

Halsted did not develop his procedure for patients with small primary tumors with no palpable lymph glands. He, and surgeons before him, rarely saw such patients, since early diagnosis was veritably unheard of. Surely, Halsted would have questioned whether a radical procedure was necessary for such patients. Certainly, surgeons in this country should have questioned it a long time ago.

A great deal of selection takes place in the management of breast cancer. Early diagnosis is clearly important. Those surgeons who select patients for "operability" and small tumors, with no or few axillary glands involved, will have the best results whatever operation is used; but their results may be irrelevant in regard to the universe of patients with breast cancer. Witness the fact that those patients who have their disease detected only by mammography (tumor not detectable on physical examination), rarely have lymph gland involvement, and have an excellent five, and we may presume, ten year survival. Therefore, it is not scientifically sound to compare data between centers, and amongst countries, unless those data were assembled in accordance with principles of good clinical trials, to sort out the influence of selection and bias.

In all the reports cited by Dr. Haagensen, including his own, biases enter into and influence the interpretation of the data. For example, Dr. Haagensen uses his population of patients who had biopsy proven disease in the internal mammary and/or supraclavicular lymph gland chain (who received radiotherapy as the primary treatment instead of surgery) as an example of the ineffectiveness of radiotherapy as a primary treatment. Here he now uses survival as his guidepost. The data he presents are misleading. Survival is bad in this group in Dr. Haagensen's study, as one would expect. The patients had proven glandular disease which, as I have said, reflects the presence of distant metastases. The survival of these patients would have been equally bad had they had a radical mastectomy; wasn't this the reason he excluded them from consideration for radical mastectomy in the first place? It is not fair, then, to use these survival data to reflect negatively on the potential effectiveness of radiotherapy, to control the local tumor, after excisional biopsy, in a group ineligible for surgery by his own criteria.

Radiotherapy, as a primary treatment, like less radical surgery of breast cancer, in my view, has not had a fair test as a means of controlling the primary cancer in patients with small lumps. Recent results

of Hellman, from the Harvard Joint Center for Radiotherapy, using radiotherapy as the primary treatment in breast cancer, demonstrate an apparent ability to achieve local control equivalent to surgery. Hellman does this while achieving extremely good cosmetic results, the lesser doses of radiation required to treat small tumors are less toxic to normal tissue than that required to treat large bulky tumors.

Where, then, is radical mastectomy really indicated? In patients without lymph gland involvement, it is very questionable as to whether a radical procedure is indicated because the disease has not spread to the axilla; in those with axillary gland involvement by itself, radical mastectomy is both too much and not enough. I, for one, am not willing to rely solely on Dr. Haagensen's survival data, excellent as they are, because I don't believe the differences between his data and that of other equally excellent surgeons, are significant, considering selection factors and individual bias. We continue to recommend mastectomy with axillary dissection (modified radical mastectomy) in many cases because of the need to know the status of the lymph glands in the axilla in regard to further decisions about postoperative treatment with drugs. We have no other reliable test to determine their status at the present time.

One of the reasons for lack of enthusiasm in studying less radical approaches for the control of local breast cancer is that they were, and are, unlikely to produce better survival results than radical mastectomy just, at best, equivalent survival with less morbidity. The most immediate pressure on the treatment of primary breast cancer, in my view, has been created by recent observations on the value of postoperative chemotherapy. The ability to prevent metastases using drugs after surgery makes further rapid exploration of less radical primary treatment more attractive. The adjuvant chemotherapy studies referred to were aimed at the unassailable fact, already referred to, that patients who have positive lymph nodes, for the most part, should be considered as having metastatic disease, even though it is not visible to the naked eye or detectable by current laboratory tests. Since these drugs were known to be effective in treating some patients with widespread, visible, metastatic breast cancer, it made sense to apply these early in the postoperative period. Actually, surgeons like Dr. Fisher, had the courage to do this as early as 1958, based on experiments by Martin and his colleagues in New York, in mice with breast cancer, showing these types of approaches were likely to be efficacious.

The results of their first study, using the old drug, thiotepa, actually were positive; but, for many years they were interpreted as "unimpressive". The reason for this interpretation was although recurrences were delayed, most treated patients eventually developed metastases. The interesting point about this old study is the positive impact of the delay in

-4-

recurrence on survival at the fifth and even the tenth year in the small group of women affected by the drug. This, ultimately, was not an unimpressive study. It is only surprising it was positive at all, considering the low dose and short term nature of the postoperative chemotherapy. However, it was still difficult, for many years, to get the medical community in this country to consider large scale adjuvant chemotherapy trials in patients with breast cancer with positive lymph glands.

There have now been about a dozen studies using adjuvant chemotherapy in the postoperative period. The majority show a positive effect. Most earlier studies had little impact on the medical practice in this country because they were uncontrolled studies, and we all recognize breast cancer to be too variable a disease to rely on data from improperly designed clinical trials. The two studies mentioned by Dr. Haagensen, the L-Pam and the CMF studies, were properly designed, carefully controlled, clinical trials and they are both clearly positive. They both clearly demonstrate a decreased recurrence rate in patients with carcinoma of the breast who have positive lymph glands. The magnitude of the prevention of recurrence in both studies cannot, in my view, fail to impact on survival at five and ten years. It is not yet possible to determine whether the drugs actually cure patients or just prevent their recurrences for longer periods of time. However, for the first time, we are getting at the heart of the problem, treatment of micrometastatic disease in patients whose tumor has spread to the lymph nodes. In my view, patients should now be offered the alternative of postoperative therapy if their lymph glands are positive. I do not believe the data are sufficiently strong, nor the long term risks of postoperative chemotherapy sufficiently clear, to offer it to patients whose lymph glands are not positive at the time of surgery.

In the past 82 years, since the description of the radical mastectomy by Halsted, the medical community at large has concentrated solely on saving the life of the patient. This is a noble venture and always thoroughly justified, however radical the approach, in the absence of viable alternatives. However, use of inductive reasoning, after a reasonable time, would have dictated we ask the question as to whether the procedures used to control local disease needed to be as radical. It took us far too long to do this, primarily because physicians were not trained in the past to do good therapeutic research rather only to deliver the therapy of their time, and many are unwilling to change.

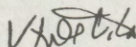
I agree with Dr. Haagensen in regard to Rabelais' statement, "Science without conscience is but ruination of the soul." But we must be careful what we call science. Some medical practices have not been developed scientifically, but by habit, and are perpetuated beyond reasonable periods of time because of the failure to use scientific inductive reasoning in clinical therapeutic research.

-5-

I believe it is, indeed, unethical for a physician to enter a patient on a clinical trial comparing two possible alternative treatments when he truly believes one of the alternatives represents a clearly inferior therapy. Clearly then, Dr. Haagensen would be unable to randomize any of his patients in a clinical trial because of his strong bias in favor of the radical mastectomy. However, many of us feel the overwhelming mass of data in the literature today supports Dr. Fisher's statement that we don't know how to treat patients with localized breast cancer; and radical mastectomy may be inferior treatment; we do know we need systemic treatment to salvage the great majority of those patients whose disease has spread to the lymph nodes and beyond; no amount of radical surgery or radiation treatment will do this. We may have that systemic treatment now, and Dr. Fisher and his colleagues have set up a series of logical studies to carefully examine less radical approaches to control the primary tumor, with and without radiotherapy and post-operative chemotherapy.

Their approach is ethical, because radical mastectomy is associated with morbidity and mortality not observed with less radical approaches; because women would prefer to save their breast if they can do so without risking their lives, and because there are already data to suggest to many of us that less radical procedures are at least as good as radical mastectomy. Most important of all they are proceeding in a scientific fashion guaranteed to provide an answer, whatever it is, to this complex and controversial question which has plagued us 50 years too long.

In my view, technology is now available to test the alternate hypothesis that we can save both the patient's life and breast; we should continue to exploit it. I have attached a recent paper of my own on this subject for your added information.



Vincent T. DeVita, Jr., M.D.
Director
Division of Cancer Treatment
National Cancer Institute

Attachment

CARCINOMA OF THE BREAST: STATUS OF ADJUVANT MEDICAL TREATMENT

Vincent T. DeVita, Jr., M.D.
Director
Division of Cancer Treatment
National Cancer Institute
Bethesda, Maryland

Introduction

In the years since 1894, after Halsted developed the radical mastectomy, the survival for patients with breast cancer improved. Then about the mid 1950's, the survival curves plateaued. Although the reason for the plateau was not fully appreciated at the time, some physicians began to intercede even then in the postoperative period with attempts to prevent the recurrence of tumor. The logic of the time dictated that the major reason for treatment failure was dislodgement of tumor cells from the primary lesion at the time of surgery, or failure to remove all evidence of tumor en bloc. Most ancillary therapeutic maneuvers, therefore, attempted to exploit local attempts to improve control, or brief systemic treatment to destroy dislodged, circulating, presumably viable, cancer cells. Furthermore, although it was appreciated that involvement of the homolateral axillary lymph nodes influenced prognosis, the true impact of this observation, and the quantitation of the effect of increasing nodal involvement on survival was not truly appreciated. The most recent, and best analyzed, data on this point are shown in table 1 from the NSABP studies (13,14). Considered as a group, patients with positive lymph nodes have almost an 80% chance of developing recurrences over a ten year period, and 67% of the recurrences occur within the first five years. Survival rates vary in inverse proportion to the recurrence rate, as would be expected. Furthermore, as shown in table 1, the relapse rate is influenced by the degree of nodal involvement as shown by the recurrence rates at five and ten years in patients with one to three positive nodes as compared to those with greater than four positive nodes.

Our knowledge of the growth characteristics of murine and human tumors and their interaction with drugs was sketchy in the late 1950's. There are now several important pieces of information which have influenced the design of newer trials employing postoperative treatment of breast and other types of cancer. First and foremost, was the realization that treatment failure in most tumors occurred as a result of continuous shedding of cells from the primary tumor (cell loss) very early in the life cycle of most cancers long before surgical manipulation (8). Although many shed cells are not viable, and many viable shed cells are undoubtedly controlled by the host's defense mechanisms, most newly diagnosed patients with breast cancer probably have micrometastases undetectable by current diagnostic techniques (25). This point is underscored by the fact that even patients without evidence of homolateral lymph node involvement have a 25 percent chance of eventually succumbing to their disease as shown in table 1 (13,14). Second, was the reaffirmation that drugs killed by first order kinetics (25). A given dose of a drug (or combination of drugs) kills a constant fraction of susceptible tumor cells, not a constant number, and the surest way to increase the killing power of drugs is to reduce the population size at risk in experimental systems (8,25). The alternative route, increasing drug doses is often limited by life threatening toxicity to the host (8). If surgically treated patients have micrometastases to account for high recurrence rates, micrometastases should be easier to control, by virtue of their smaller number, if some form of effective systemic treatment is available. Cell kinetic studies have provided additional useful data (8). Growth characteristics of populations of tumor cells vary with the size of the

population (8). Tumor growth is logarithmic in its early stages, but is exponentially retarded as tumor volume increases (8,25). As a tumor mass increases in size, the number of cells in a growth cycle decreases. Non-dividing cells are less vulnerable to all treatments, particularly radiotherapy and chemotherapy, although immunotherapy may be a possible exception. In addition to the advantage of a small tumor burden micrometastases might be expected to be in a kinetically vulnerable state for drug treatment in the postoperative period. Another point. Even the most rapidly growing experimental tumor systems can rarely be cured with brief exposures to chemotherapy, even though the cell cycle length of mouse tumors and normal tissues are far briefer than in the human counterpart. It was and still remains unrealistic to assume that brief exposure to drugs, or exposure to drugs at widely spaced intervals after surgery would place all micrometastases at equal risk of being destroyed without allowing some cells to escape drug exposure, or repair drug induced damage, and regrow to lethal levels. Finally, and still a very important point even in the selection of drugs for today's studies, is the question of the level of activity for a given agent (or agents) required in patients with advanced tumors, before the treatment program can be considered ready for use as an adjuvant to surgery. It is conceivable drugs shown to be inactive in kinetically unfavorable, advanced tumors would be active against fewer and more vulnerable micrometastases. The answer to this latter question is as yet unknown, but the current practice is to employ as adjuvants only agents known to be effective in patients with advanced cancer of the same histologic type. Again, the use of immunotherapy, which, in experimental systems, is only effective against small number of cells, may be a possible exception. Taking these

points into consideration, the more recent, successful, adjuvant drug treatment programs have employed proper stratification of patients in randomized controlled trials, with known active drugs, administered in full doses, in proper schedules, for prolonged periods of time, in patient populations with a known high risk of recurrence (3,12).

One final word about other treatment adjuvant approaches to breast cancer. It is now abundantly clear that the plight of patients with operable breast cancer and positive homolateral axillary lymph nodes has not been significantly influenced by aggressive attempts to control the tumor locally with either more radical surgical procedures or radiotherapy (10,14,16,30). Therapeutic trials in progress, examining lesser surgical treatments of breast cancer have not as yet demonstrated any advantages for more radical surgical procedures in either stage I or II breast cancer (FISHER, B., Personal Communication). Also, sufficiently good controlled clinical trials have demonstrated that the routine use of postoperative radiotherapy does not alter survival of patients with breast cancer (10,14,16). Both radical surgery and radiotherapy fail to deal with the problem of micrometastases at sites remote from the chest wall. It is also abundantly clear that postoperative radiotherapy does, indeed, decrease the incidence of local recurrences. However, only one-third of operated patients develop local recurrences; in two-thirds local recurrences can be controlled by radiotherapy at the time they appear, and the remainder rarely die as a result of local disease. It seems unreasonable, considering the complications, expense, and inconvenience, of postoperative radiotherapy and the potential interference with other treatment programs, to continue to subject patients with breast cancer

to routine postoperative radiotherapy to deal with a problem which will cause major morbidity in only one-ninth of the population of operable breast cancer patients. Although postoperative radiotherapy, it can be argued, will further reduce the tumor burden, and thus aid other adjuvant programs, this point is as yet unproven. It is possible radiotherapy might interfere with the killing effects of drugs or immunotherapy and leave a larger residual nest of viable cells.

In this authors view, the apparent success of the adjuvant treatment programs to be described below should relegate postoperative radiotherapy to the position of an investigative tool in studies to determine its value in conjunction with chemotherapeutic and immunotherapeutic adjuvant treatment programs.

Review of earlier published studies in adjuvant chemotherapy of breast cancer

A number of studies have been initiated using post-operative chemotherapy in patients with various stages of breast cancers. The results of older trials are summarized in table 2. In eight of the eleven trials, the authors referenced in table 2 reported a decreased relapse rate in the chemotherapy arm, in either all the patients, or in a subset of the population. In five of the studies, this decreased or delayed recurrence rate was associated with improved survival. In the first six studies listed in table 2, you should note the extremely short-term nature of the chemotherapy, usually a few days to a few weeks. The last five studies employed chemotherapy from six months to one year, but in only three was the chemotherapy given with sufficient intensity, or with proper drugs and doses which would now be considered appropriate

for treatment of breast cancer. The studies of Donegan (9) employing weekly thiotepea for seven months, and the studies of ANSFIELD, (1) and RAMERIZ (21), employing 5-Fluorouracil for one year are exceptions in regard to duration of therapy but have other deficiencies. The study of DONEGAN revealed no difference in recurrence rate or survival in the treated or control population, while the uncontrolled studies of ANSFIELD and RAMERIZ, from Wisconsin, showed a decrease in recurrence rates. The criteria for patient selection was inconsistent, some studies included patients with negative axillary lymph nodes (stage I), as well as those with positive nodes (stage II), and often detailed data are unavailable in the published reports. In some cases, the surgical technique varied considerably within a given study. Given the lack of adequate stratification in the randomization procedures employed, the numbers involved, in most studies, were inadequate to draw firm conclusions. The later studies from the Wisconsin group were uncontrolled, or used historical controls, an approach which should be considered inadequate in the study of adjuvant treatment of a chronic disease like breast cancer. In general, the data reported were not given enough detail, and accurate statistical evaluation was carried out only in the minority of studies. Even if these studies would have been properly designed, the type and duration of chemotherapy offered in the majority of studies would now be considered inadequate

The best data in the studies reported in table 2 are that of FISHER et al. (13). These data were derived from a large randomized study which now has had a ten year followup. The population is large enough to draw valid conclusions. It examined the effects of a single full

dose of thiotepa as adjuvant treatment. When considered as a whole, there was no decrease in recurrence rate in the group treated with thiotepa; when examined in subsets, the data show a diminished recurrence rate in the population of premenopausal women with four or more positive homolateral axillary lymph nodes, in the interval between 18 and 36 months from the time of surgery. Survival data at five and ten years revealed an increased fraction of premenopausal women with positive lymph nodes treated with thiotepa surviving at both points in time when compared to controls. Even though there were a large number of patients randomized in this study, the subset populations in question are small, and although the data are significant, confirmation was necessary. Here again, the duration of chemotherapy would now be considered totally inadequate. Thiotepa was administered only in the immediate postoperative period with no further therapy. Another criticism of this study relates to the fact that premenopausal women might have had a drug induced menopause to account for the delay in recurrences. While this does not seem a likely explanation for the beneficial results in premenopausal women, there are insufficient data in the thiotepa study to rule out this possibility. The initial feeling that this study, and the others referred to above, were negative, may have been significant in decreasing the interest in further drug adjuvant studies until sufficient laboratory data rekindled investigations.

Recent studies with adjuvant chemotherapy in breast cancer

This generation of prospective randomized adjuvant trials in breast cancer began with the studies started in the USA on September 22, 1972 (12)

and in Milan, Italy, on June 1, 1973 respectively (3). L-Phenylalanine mustard (L-PAM) was selected for several reasons. Although it was not the most commonly used agent in advanced carcinoma of the breast, it was a member of a class of agents known to be active (alkylating agents) and, when used in patients with systemic disease it was clearly capable of producing partial remissions. Information was already available in regard to the use of the anti-metabolite 5-Fluorouracil (13) suggesting that it might not be beneficial in the postoperative adjuvant period. L-PAM was also easily tolerated, produced little nausea and vomiting, no alopecia, was easily manageable and produced predictable effects on the bone marrow.

The second study used combination chemotherapy as an adjunctive treatment. In recent years, it has become apparent that the use of combination chemotherapy in the treatment of patients with advanced disease was superior to single agents (5). In 1970, the staff of the Medicine Branch, National Cancer Institute, designed a combination chemotherapy program which would incorporate some of the features of the successful drug combinations used in the treatment of lymphomas. It differed from other combinations used for breast cancer at the time, in that full doses of chemotherapeutic agents would be given in two week cycles, alternating with rest periods, to allow recovery of the bone marrow and immunologic systems of the patient between cycles of treatment. While this combination was designed, and initially tested in patients with advanced disease, it was the intent of the investigators to develop a combination which could be tolerably used in patients in the postoperative period (6). The initial combination of cyclophosphamide, methotrexate,

fluorouracil, and prednisone, CMF (P), proved as effective as any combination reported up to that time (5,6). Twenty percent of patients with advanced metastatic carcinoma of the breast achieved complete remission, a figure that still compares favorably to all other combinations, while overall, 68% of patients responded with useful clinical responses. Some complete remissions continued after therapy was discontinued for as long as 2 1/2 to 3 years. Since the adjuvant study with L-PAM was in progress, it was reasoned that the next logical sequence on the path to the use of the CMF program as an adjuvant treatment was to compare this drug combination's effects with those of L-PAM in patients with advanced metastatic disease. This second study has been completed (26). The results are of interest. First, the doses were modified downward to make the combination more tolerable in a wider range of patients (Figure 1). Second, it was reasoned that prednisone probably added little to the combination and its use was discontinued. The results show that CMF produced twice as many responses as L-PAM alone, but more importantly, four times the number of complete remissions were achieved using CMF when compared to L-PAM. As in most chemotherapeutic studies using drug combinations, the complete remissions were seen mostly in patients with soft tissue, lymph node and pulmonary involvement. Bony lesions remain difficult to treat in patients with advanced disease. Although bone healing has now been observed, the data with L-PAM were consistent with the older literature, in that, it was exceedingly uncommon in the past to see reports of complete remissions with single drug treatment of advanced breast cancer. It also should be noted that the results with L-PAM confirmed that the drug was indeed an active agent for treatment of patients with advanced breast cancer and substantiated the logic of its use as an adjuvant treatment.

With these data in hand, the Division of Cancer Treatment, NCI supported a study at the National Cancer Institute in Milan, Italy, using CMF as a postoperative adjuvant treatment, compared to a control, untreated patient population. Both the L-PAM and CMF adjuvant studies have now been completed (3,12). Both trials were very closely matched in terms of criteria for patient selection. They differed in regard to the chemotherapy employed. Within four weeks of radical, or modified radical, mastectomy in the FISHER study, patients were randomized between a placebo and cyclical administration of L-PAM at a dose of 0.15 mg/kg per day for five consecutive days every six weeks. In the absence of documented evidence of treatment failure, chemotherapy and placebo were given for two consecutive years. In the study performed at the National Cancer Institute of Milan, Italy, patients were randomized to no further therapy after mastectomy, or to the CMF program as shown in figure 1. Doses were adjusted according to a sliding scale at the beginning of each subsequent cycle (3,5,6). In the absence of documented recurrence, CMF was continued for a minimum of one year.

The results of the L-PAM study were published in January of 1975 (12) and can be summarized as follows. In 108 patients receiving placebo, followed on the average of about eighteen months, 22% developed recurrences, while only 9.7% of 103 women receiving L-PAM had recurrences. A statistically significant difference was demonstrated in favor of L-PAM in terms of disease-free survival. In premenopausal women, the difference with respect to disease-free survival, of the treated and placebo group, was significant at a P value of less than 0.008. While a similar trend was observed in postmenopausal women, the differences at the time of the

report were not statistically significant. In addition, although there was a trend in favor of the effect of L-PAM in patients with 1-3 positive nodes, the results were not significant at the time of analysis.

The CMF adjuvant study has not yet been published in its entirety (3). The characteristics of patients with treatment failures in the CMF study are shown in table 3. The average followup time at this point is approximately two years. All sub-groups show significant differences in favor of adjuvant chemotherapy. The difference in the recurrence rate between CMF and controls is highly significant in the group of patients with four or more axillary nodes (P value less than 0.0005). In contrast to the L-PAM study reported by FISHER (12), the study of BONADONNA et al. (3) shows a significant difference in favor of CMF, both in those patients with less than four positive homolateral lymph nodes and in patients in the postmenopausal category. This latter point provides compelling evidence that the drug effects on ovarian function cannot be the sole reason for the positive effects observed. Table 4 illustrates some of these data from the CMF study. A significant difference is seen in the recurrence rate, even in patients with a single lymph node involved. It is also of interest, as shown in table 3, that data from the CMF study shows the proportion of failures in both the treated and control population occurred more often in patients subjected to extended radical mastectomy when compared to those operated on with conventional radical mastectomy (P value less than 0.05). Bonadonna has made an important comparison between the L-PAM and CMF combination as shown in table 5 (3). Since the stratification of patients in both studies was equivalent, these interstudy comparisons have added meaning. Within the limits of retrospective comparison, available data would indicate, that multiple drug

treatment is providing results superior to the use of single agent chemotherapy in decreasing the failure rate after radical mastectomy. Except in the category of premenopausal women, the advantage in favor of CMF appears in all subgroups of patients. However, with additional followup of the L-PAM study, the positive trend in postmenopausal women, and those premenopausal women with less than four positive lymph nodes, has increased and, has reached significance in favor of L-PAM (FISHER, B., Personal Communication). In both studies, relapses in the control population tend to begin at a very early time after mastectomy, while in the adjuvant chemotherapy group recurrences where they occur are delayed. In addition, in the Bonadonna study, further recurrences have not been noted beyond the nine month point of chemotherapy.

Analysis of the distribution of sites of relapse in the CMF study indicates that 80% of patients who develop recurrences do so at distant sites. Multiple relapses were observed in 28% of patients. In only 23%, of the total population with treatment failures, did the initial recurrence occur in local or regional areas (those areas usually encompassed by postoperative radiotherapy). In four of these ten patients, with local or regional recurrences, disseminated disease was detected within two months from the initial recurrence.

At this point in time it is difficult to place much emphasis on survival data due to the short followup. However, when one reflects on the results of the thiotepa study (13), it is apparent that the results of prevention of recurrences for even a short span of eighteen months had a significant impact on survival. It is, therefore, difficult to imagine the effects observed in the L-PAM and CMF studies will not eventually be associated with a significant positive impact on survival.

Toxicity

In the L-PAM study (12), sixty percent of patients had some degree of leukopenia. Thrombocytopenia was not a clinical problem over the time frame observed. About one-third of patients experienced nausea. On the whole, since alopecia was not produced and vomiting was rarely associated with the use of L-PAM, this type of treatment was well tolerated and acceptable to patients who were otherwise feeling well.

In the CMF study, side effects were more numerous. Nausea and vomiting were a more prominent side effect, appearing within a few hours in most patients. In BONADONNA's experience (3), about one-third of patients are reluctant to continue therapy and must be continuously urged to take the treatment at the recommended doses. Hair loss occurred in 57% of patients and stomatitis in 18%. However, pronounced alopecia was rare. Cystitis due to cyclophosphamide was observed in 30% of patients. Treatment produced amenorrhea in 54% of premenopausal patients, but in one-third of these patients, menses reappeared after treatment was stopped. Whether amenorrhea is permanent in the remaining group is uncertain. Cyclophosphamide, the drug most probably responsible for this effect has been reported to produce permanent ovarian failure (28).

Myelosuppression was the dose limiting factor in the Italian study. Leukopenia occurred in 68% of patients and thrombocytopenia in 66%. However, it should be emphasized that in no case was platelet transfusion support necessary nor did bleeding occur and infectious complications were not observed. Thus, in spite of the greater difficulty administering CMF, when compared to L-PAM, CMF can be given by skilled therapists without significant risk to the patients. It has been our experience

that a given dose of a single drug or combination of drugs, including CMF, is better tolerated by patients free of visible tumor than those with metastatic disease (5,6). Most of the projected doses of each drug were given (3). For 12 cycles patients received 81% of the projected full dose of methotrexate and 5-Fluorouracil and 76% of cyclophosphamide. Only ten patients refused to complete treatment, mainly for psychological reasons.

Conclusions

Current examples of ongoing clinical trials with adjuvant chemotherapy and/or immunotherapy are illustrated in table 6. There are several important questions asked. What is the role of chemotherapy plus adjuvant endocrine manipulation? Although good controlled trials have failed to demonstrate the value of postoperative adjuvant endocrine therapy (17,22), with the identification of the importance of estrogen binding proteins in predicting responses in advanced breast cancer, a reanalysis of the use of endocrine manipulation, with and without chemotherapy, in the postoperative period, seems in order. It will be difficult to improve on the small relapse rate observed using CMF as an adjuvant treatment (3). However, it is worthwhile searching for a drug combination with less toxicity than CMF to make the postoperative treatment easier. In addition, immunotherapy is being evaluated at the University of California and added to the CMF program as shown in table 6. Subsequent studies at the National Cancer Institutê, in Milan, will examine the minimal duration of CMF therapy required to produce effects equivalent to 12 months of treatment.

Although it may seem far afield, one of the central questions raised by successful adjuvant chemotherapy is the impact it will eventually have on the selection of the primary surgical procedure. Progress is somewhat inhibited by our inability to predict the status of axillary lymph nodes. There is, at present, no reliable test to determine whether the lymph nodes are involved by tumor without removing them at the time of surgery, although studies are in progress examining the use of chemical markers to predict nodal involvement (29). This information is required to evaluate the efficacy of the various adjuvant treatment programs under consideration. However, should studies now in progress, testing the efficacy of lesser surgical procedures, continue to show that the lesser procedures are as good as more radical surgery; and the good results with adjuvant chemotherapy continue, the way of the future in patients with breast cancer seems clear. If the risk of adjuvant treatment in patients with and without positive nodes could be shown to be less than the long term benefits, a much lesser surgical procedure, coupled with systemic treatment may become the treatment of choice. It is here that radiotherapy may play an important role. Delivery of radiotherapy with more sophisticated equipment, which would provide control of the local tumor, and, in contrast to surgery, preserve most of the normal tissue, needs to be investigated. It should be emphasized, however, that although these approaches are attractive, they should not be embarked upon without adequate data. The risk of carcinogenesis as a result of treatment may be significant (2,4,24). It is conceivable, that although surgery, radiotherapy, and chemotherapy of the types described above, may not be overly risky in the long run, combinations of radiotherapy and chemotherapy with minimal surgical

procedures could lead to an inordinate risk of carcinogenesis. All these questions must be answered with properly designed, prospective clinical trials. Given the long, drawn-out, natural history of carcinoma of the breast, many of these studies, recently started, or soon to be embarked upon, will take five to ten years to provide sufficient data.

The most important advance in carcinoma of the breast, in my view, has been the willingness of physicians and patients to take part in such clinical trials. Indeed, patients are demanding such trials. Patients, and their physicians, should continue to be urged to take part in clinical trials to help answer some of these very important questions in this common disease of women.

Hopefully with the encouragement derived from the current studies we should now be able to concentrate on the problem foremost in the patients mind, "How can I save my breast, or as much of my breast as possible, without losing my life".

TABLE 1
EFFECT OF LYMPH NODE INVOLVEMENT
UPON RECURRENCE RATE AND SURVIVAL

IPSILATERAL AXILLARY NODES	RELAPSE RATE (%)			SURVIVAL (%)		
	18 Mos.	5 Yr	10 Yr	5 Yr	10 Yr	
N-	5	21	24	76	65	
N+	33	67	76	46	25	
(1-3)	13	53	65	62	38	
(<u>></u> 4)	52	80	86	31	13	
All patients	17	45	50	61	46	

Modified from B. Fisher (13,14)

TABLE 2
SUMMARY OF RESULTS OBTAINED WITH POSTOPERATIVE CHEMOTHERAPY

PRINCIPLE AUTHOR	REFERENCE	COUNTRY	STAGE	NO. OF PATIENTS CONTROL	TREATED	TREATMENT	DURATION OF CHEMOTHERAPY	RELAPSE RATE	SURVIVAL
FISHER	13	USA	I - II	207	450	RM+FU		Decreased at 3 yr. in > 4N+	NA
				603	1078	RM+TSPA	3 days	Delayed in > 4N+ Pre- menopausal	Increased
GARIN	15	USSR	I - II	--	698	RM+TSPA RM+CTX	14 days	Decreased Increased	NA NA
MANSSEN	19	DENMARK	I - II	554	534	M*+CTX	6 days	Decreased	No difference
FIRNEY	11	ENGLAND	I - II	40	43	M*+CTX	10 days	Increased	Decreased in Stage II
RIECHE	23	GERMANY	I, II, III	144	143	RM+CTX	2 Mos.	Decreased in N+	Increased in N+
YOSHIDA	29	JAPAN	NA	--	167	RM+MITO	2 Wks.	NA	No difference

M* = Simple, Modified Radical or Radical Mastectomy
RM = Radical Mastectomy
NA = Data not yet available

FU: 5 Fluorouracil
TSPA: Triethylene Thiophosphoramide
CTX: Cyclophosphamide
Mito: Mitomycin C

TABLE 2 (continued)
SUMMARY OF RESULTS OBTAINED WITH POSTOPERATIVE CHEMOTHERAPY

PRINCIPLE AUTHOR	REFERENCE	COUNTRY	STAGE	NO. OF PATIENTS CONTROL	TREATED	TREATMENT	DURATION OF CHEMOTHERAPY	RELAPSE RATE	SURVIVAL
DONEGAN	9	USA	I - II	90	76	RM+TSPA	Wkly. x 7 Mos.	No difference	No difference
MRAZEK	20	USA	I - II	78	78	RM+HN ₂	q 3 Mos. x 1 Yr.	Decreased	Increased
KHOLDIN	18	USSR	I - II	--	392	RM+TSPA +CTX (+ Endo- crine)	6 Mos. -	Decreased	Increased
ANSFIELD	1	USA	II	--	60	RM+FU	1 Year	Decreased	Increased
RAMIREZ	21	USA	II	--	35	RM+FU	1 Year	Decreased	NA

M* = Simple Modified Radical or Radical Mastectomy

RM = Radical Mastectomy

NA = Data not yet available

FU: 5 Fluorouracil
TSPA: Triethylene Thiophosphoramide
CTX: Cyclophosphamide
Mito: Mitomycin C

TABLE 3

CHARACTERISTICS OF PATIENTS WITH TREATMENT FAILURE IN THE CMF STUDY*

	EVALUABLE PATIENTS			
	CONTROLS		CMF	
	No.	%	No.	%
TOTAL WITH RELAPSE	38/165	23	5/185	2.7
Axillary nodes	1-3	15*	2/124	1.6
	≥ 4	42*	3/61	5
Age (years)	≤ 49	24	3/86	3.4
	≥ 50	22.5	2/99	2
Menopause	pre	24	3/85	3.5
	post	22	2/100	2
Mastectomy	radical	17.5**	4/128	3.1
	enlarged	38**	1/57	1.7

From Bonadonna et al (3) with permission of the authors.
 All differences between controls and CMF treated patients are
 significant at the $P = < 0.005$ Level.

*One to three vs. four or more $P < 0.005$

**Radical vs. enlarged mastectomy $P < 0.05$

TABLE 4

PERCENT OF TREATMENT FAILURES RELATED TO THE NUMBER OF
HISTOLOGICALLY INVOLVED AXILLARY LYMPH NODES

POSITIVE NODES		FAILURE PROPORTIONS	FAILURE RATE*	RATIO
1	Controls CMF	11/69= 16% 1/59= 1.6%	130 15	8.7
2	Controls CMF	2/28= 7.1% 0/43= -	58 -	-
3	Controls CMF	4/18= 22% 1/22= 4.5%	197 42	4.7
4	Controls CMF	3/16= 18% 1/17= 5.8%	171 54	3.2
5-6	Controls CMF	9/16= 56% 1/11= 9%	675 104	6.5
≥ 7	Controls CMF	6/18= 33% 1/33= 3%	481 35	13.7

* Per year per thousand patients. From Bonadonna et al
(3). Published with permission of the authors.

TABLE 5

COMPARATIVE RECURRENCE RATES BETWEEN SINGLE AGENT CHEMOTHERAPY (L-PAM) AND COMBINATION CHEMOTHERAPY (CMF) USED IN THE POSTOPERATIVE TREATMENT OF STAGE II BREAST CANCER

TREATMENT	TOTAL EVALUABLE PATIENTS	PERCENT OBSERVED RECURRENCES CONTROL VS. CHEMOTHERAPY GROUP				
		TOTAL	1-3 + Nodes	4 + Nodes	Pre- Menopausal	Post- Menopausal
RM + L-PAM	211	22 vs. 9.7	6.1 vs. 1.9	34 vs. 18	30 vs. 3	21 vs. 11
RM + CMF	350	23 vs. 2.7	15 vs. 1.6	42 vs. 5	24 vs. 3.5	22 vs. 2

From Bonadonna et. al (3)

TABLE 6

EXAMPLES OF ONGOING CONTROLLED TRIALS WITH PROLONGED ADJUVANT
THERAPY IN PRIMARY BREAST CANCER WITH POSITIVE AXILLARY NODES

GROUP	TYPE OF TREATMENT	DURATION
NSABP, ECOG, COG	R $\begin{cases} \text{Placebo} \\ \text{L-PAM} \end{cases}$	2 years
Guy's Hospital (England)	R $\begin{cases} \text{Placebo} \\ \text{L-PAM} \end{cases}$	12 cycles
Milan Cancer Institute (Italy)	R $\begin{cases} \text{Control} \\ \text{CMF} \end{cases}$	12 cycles
NSABP, ECOG, COG	R $\begin{cases} \text{L-PAM} \\ \text{L-PAM plus Fu} \end{cases}$	2 years
Mayo Clinic	R $\begin{cases} \text{RT} \\ \text{CFP} \\ \text{RT plus CFP} \end{cases}$	1 year
Univ. of California, UCLA	R $\begin{cases} \text{BCG plus CMF} \\ \text{BCG plus CMF plus TC} \end{cases}$	1 year
Memorial Hospital	R $\begin{cases} \text{RT} \\ \text{CbMF} \\ \text{Levamisole} \end{cases}$	2 years
Case Western Reserve	R $\begin{cases} \text{Control} \\ \text{CMF plus Tamoxifen} \\ \text{CMF plus Tamoxifen plus BCG} \end{cases}$	2 years
NCI, Division of Cancer Treatment	R $\begin{cases} \text{L-PAM} \\ \text{CMF} \\ \text{CMF plus C. Parvum} \end{cases}$	2 years

Abbreviations: RT = radiotherapy; L-PAM = melphalan; C = cyclophosphamide;
M = methotrexate; F = fluorouracil; P = prednisone; Cb = chlorambucil;
TC = allogeneic tumor cell.

NSABP = National Surgical Adjuvant Breast Project
ECOG = Eastern Cooperative Oncology Group
COG = Central Oncology Group

From Carbone, P. P. (7)

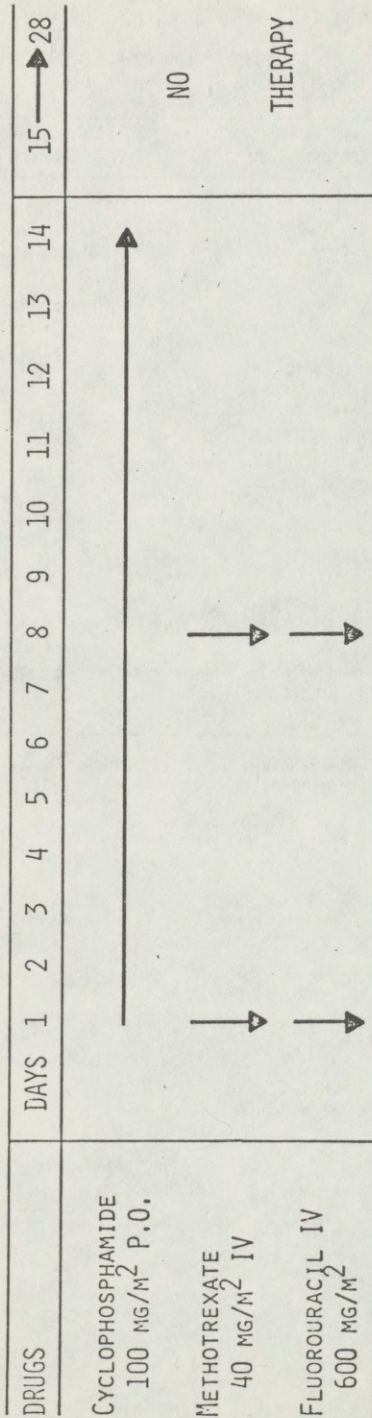


FIG. 1 A SINGLE CYCLE OF CMF; CYCLES REPEATED AT MONTHLY INTERVALS WITH DOSE ADJUSTMENTS MADE ON BASIS OF MYELOSUPPRESSION. DOSES MODIFIED FOR ADJUVANT USE FROM CANELLOS ET. AL (5,6)

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Senator KENNEDY. Thank you very much. The subcommittee stands in adjournment.
[The subcommittee adjourned at 1 p.m.]

