DOCUMENT RESUME

ED 255 486 SP 025 895

TITLE Progress in Controlling Breast Cancer. Hearing before the Subcommittee on Health and Long-Term Care of the Select Committee on Aging. House of Representatives, Ninety-Eighth Congress, Second Session.
INSTITUTION Congress of the U.S., Washington, D.C.
PUB DATE 28 Jun 84
NOTE 297p.; Portions of document contain small print.
PUB TYPE Legal/Legislative/Regulatory Materials (090)

EDRS PRICE MF01/PC12 Plus Postage.
DESCRIPTORS *Cancer; *Disease Control; *Disease Incidence; Federal Legislation; Females; *Government Role; Medical Services; Older Adults; Prevention; Public Health; *Research Needs
IDENTIFIERS *Breast Cancer

ABSTRACT

This report contains testimony on the subject of breast cancer. Under consideration was a proposed bill that will assure women that physicians and surgeons inform breast cancer patients of alternative, effective, methods of treatment and will ensure that the woman will have to give her informed consent before any treatment is initiated. Also considered was a bill which will require Medicare to provide coverage for routine cancer screening. The need for research on a cancer vaccine was also under consideration. Witnesses included women who had personally experienced breast cancer, experts on the treatment of cancer, and cancer researchers. (JD)

PROGRESS IN CONTROLLING BREAST CANCER

HEARING

BEFORE THE

SUBCOMMITTEE ON HEALTH AND LONG-TERM CARE

OF THE

SELECT COMMITTEE ON AGING HOUSE OF REPRESENTATIVES

NINETY-EIGHTH CONGRESS

SECOND SESSION

JUNE 28, 1984

Printed for the use of the Select Committee on Aging

Comm. Pub. No. 98-464

U.S. GOVERNMENT PRINTING OFFICE
WASHINGTON : 1984

39-184 O

SELECT COMMITTEE ON AGING

EDWARD R. ROYBAL, California, *Chairman*

CLAUDE PEPPER, Florida
MARIO BIAGGI, New York
IKE ANDREWS, North Carolina
DON BONKER, Washington
THOMAS J. DOWNEY, New York
JAMES J. FLORIO, New Jersey
HAROLD E. FORD, Tennessee
WILLIAM J. HUGHES, New Jersey
MARILYN LLOYD, Tennessee
STAN LUNDINE, New York
MARY ROSE OAKAR, Ohio
THOMAS A. LUKEN, Ohio
GERALDINE A. FERRARO, New York
BEVERLY B. BYRON, Maryland
WILLIAM R. RATCHFORD, Connecticut
DAN MICA, Florida
HENRY A. WAXMAN, California
MIKE SYNAR, Oklahoma
BUTLER DERRICK, South Carolina
BRUCE F. VENTO, Minnesota
BARNEY FRANK, Massachusetts
TOM LANTOS, California
RON WYDEN, Oregon
DONALD JOSEPH ALBOSTA, Michigan
GEO. W. CROCKETT, JR., Michigan
WILLIAM HILL BONER, Tennessee
IKE SKELTON, Missouri
DENNIS M. HERTEL, Michigan
ROBERT A. BORSKI, Pennsylvania
FREDERICK C. (RICK) BOUCHER, Virginia
BEN ERDREICH, Alabama
BUDDY MacKAY, Florida
HARRY M. REID, Nevada
NORMAN SISISKY, Virginia
TOM VANDERGRIFF, Texas
ROBERT E. WISE, JR., West Virginia
BILL RICHARDSON, New Mexico

MATTHEW J. RINALDO, New Jersey,
Ranking Minority Member
JOHN PAUL HAMMERSCHMIDT, Arkansas
RALPH REGULA, Ohio
NORMAN D. SHUMWAY, California
OLYMPIA J. SNOWE, Maine
JAMES M. JEFFORDS, Vermont
THOMAS J. TAUKE, Iowa
JUDD GREGG, New Hampshire
GEORGE C. WORTLEY, New York
HAL DAUB, Nebraska
LARRY E. CRAIG, Idaho
COOPER EVANS, Iowa
JIM COURTER, New Jersey
LYLE WILLIAMS, Ohio
CLAUDINE SCHNEIDER, Rhode Island
THOMAS J. RIDGE, Pennsylvania
JOHN McCAIN, Arizona
MICHAEL BILIRAKIS, Florida
GEORGE W. GEKAS, Pennsylvania
MARK D. SILJANDER, Michigan
CHRISTOPHER H. SMITH, New Jersey
MICHAEL DeWINE, Ohio

JORGE J. LAMBRINOS, *Staff Director*
PAUL SCHLEGEL, *Minority Staff Director*

SUBCOMMITTEE ON HEALTH AND LONG-TERM CARE

CLAUDE PEPPER, Florida, *Chairman*

IKE ANDREWS, North Carolina
JAMES J. FLORIO, New Jersey
HAROLD E. FORD, Tennessee
MARILYN LLOYD, Tennessee
MARY ROSE OAKAR, Ohio
THOMAS A. LUKEN, Ohio
WILLIAM R. RATCHFORD, Connecticut
BUTLER DERRICK, South Carolina
RON WYDEN, Oregon
GERALDINE A. FERRARO, New York
HENRY A. WAXMAN, California
BRUCE F. VENTO, Minnesota
IKE SKELTON, Missouri
DENNIS M. HERTEL, Michigan
ROBERT A. BORSKI, Pennsylvania
EDWARD R. ROYBAL, California
(Ex Officio)

RALPH REGULA, Ohio,
Ranking Minority Member
THOMAS J. TAUKE, Iowa
GEORGE C. WORTLEY, New York
HAL DAUB, Nebraska
LARRY E. CRAIG, Idaho
JIM COURTER, New Jersey
THOMAS J. RIDGE, Pennsylvania
JOHN McCAIN, Arizona
MICHAEL BILIRAKIS, Florida
MICHAEL DeWINE, Ohio
MATTHEW J. RINALDO, New Jersey
(Ex Officio)

BILL HALAMANDARIS, *Staff Director*
KATHLEEN GARDNER CRAVEDI, *Assistant Staff Director*
MARK BENEDICT, L.L.B., *Minority Staff Director*

CONTENTS

Members Opening Statements

	Page
Chairman Claude Pepper	1
Mary Rose Oakar	4
Ralph Regula	8

Chronological List of Witnesses

Panel one:	
Irene Cohen, Deerfield Beach, FL	37
Doris E. Levin, Rockville, MD	38
Ruth Spear, New York, NY	39
Janet Nixon, Chicago, IL	43
Carolyn Alford, Midlothian, VA	45
Rose Kushner, Kensington, MD	49
Panel two:	
Ernst L. Wynder, M.D., president, American Health Foundation, New York, NY	61
George Crile, Jr., M.D., emeritus clinician, Cleveland Clinic, Cleveland, OH	65
Barbara Threatt, M.D., Institute of Social Research and Michigan Cancer Foundation, University of Michigan, Ann Arbor, MI	70
Charles Hubay, M.D., professor of surgery, Case Western Reserve School of Medicine, Cleveland, OH	92
Panel three:	
Alfred Knudson, M.D., Ph.D., senior member, Fox-Chase Cancer Center, Institute for Cancer Research, Philadelphia, PA	104
Philip Strax, M.D., Director, Guttman Breast Cancer Detection Clinic, New York, NY	111
William Feller, M.D., director, Georgetown University Breast Cancer Followup Study Project, Washington, DC	114

Appendix

Appendix 1—Material submitted for the record by Carolyn Alford, Midlothian, VA	151
Appendix 2—Material submitted for the record by Charles Hubay, M.D	182
Appendix 3—Additional material submitted for the record by Virginia C. Livingston-Wheeler, M.D., the Livingston-Wheeler Medical Clinic, San Diego, CA	262

PROGRESS IN CONTROLLING BREAST CANCER

HOUSE OF REPRESENTATIVES,
SELECT COMMITTEE ON AGING,
SUBCOMMITTEE ON HEALTH AND LONG-TERM CARE,
Washington, DC.

The subcommittee met, pursuant to notice, in room 2212, Rayburn House Office Building, Hon. Claude Pepper (chairman of the subcommittee) presiding.

Members present: Representatives Pepper of Florida, Andrews of North Carolina, and Oakar of Ohio.

Staff present: Bill Halamandaris, staff director; Kathleen Gardner Cravedi, assistant staff director; Melanie Modlin, executive assistant; Mark Benedict, minority staff director; Susan Roland, assistant minority staff director; Mary-Lou Stone, congressional fellow; Stephen Bernstein, Susan Ayanian, Margaret Campell, Steven Edelstein, Robin Morgan, Beth Hernandez, Mark Prashker, interns; Dr. Lewis Kuller, congressional fellow.

OPENING STATEMENT OF CHAIRMAN CLAUDE PEPPER

Mr. PEPPER. The committee will come to order, please.

Ladies and gentlemen, members of the committee, I want to commend in the warmest way my great colleague, Ms. Mary Rose Oakar, for calling this hearing, which may be one of the most meaningful hearings we shall have. Hopefully this hearing will generate some ideas, suggestions, and proposals that will save the lives of many of our citizens and many of our loved ones.

There are some of us who wish there had been hearings on breast cancer long ago. The senior lady in my office, a wonderful lady who had been with me 20 years, was one of the victims of that terrible disease, and many others who are very close to me have had the same tragedy.

But we could have gained the knowledge that could have spared us and prevented those whom we love so much from being lost.

Cancer is a great concern to the elderly people of this country, and rightfully so. Persons over 54 years of age constitute 81 percent of all cancer deaths, and as you know, over 400,000 people in America die every year from cancer. People over the age of 65 account for 60 percent of all cancer deaths.

The subject of today's hearing, breast cancer, is of particular concern to our elderly, especially our elderly women. One-quarter of the 35,640 women who died of breast cancer in 1980 were over the age of 75. Breast cancer is an epidemic in the United States—1 out of every 12 women will get it. And over 1½ million women have or have had breast cancer in the United States today. Practically

every family has, unfortunately, been affected by this disease, which is one of the most serious health problems that we have among women in our country.

In spite of major research efforts which we will hear about today, the number of new cases of breast cancer, over 115,000 each year, and the number of breast cancer deaths, about 37,000 each year, have not been reduced. It is scandalous that this terrible disease remains uncontrolled, when we know that a few procedures now available could reduce deaths from breast cancer by 30 to 40 percent, saving at least 10,000 lives a year. And I will add that while I was in the Senate I saw five Senators die from cancer, all of whom had opposed an increase in the appropriations to fight cancer. They said the Government couldn't afford it, that we didn't have enough money to save the lives of even a few of those 400,000 a year who die.

Less than 20 percent of all women seek preventive screening for early detection of breast cancer, on an annual basis. Most women wait until symptoms express themselves, and by then the prospects for survival are substantially reduced.

One of the things we pointed out recently, when we had the hearing on medical quackery, was that the quacks sometimes induce a woman to wait too long to get a test. If she were able to get a test earlier, before the disease progressed, in a great many instances she would be likely to be saved. Too often the quacks deter her from going through orthodox and approved procedures, and too often make her wait too late.

The Health Insurance Plan of Greater New York, a pioneer HMO, showed that screening healthy women with breast x rays and physical exams could reduce breast cancer by over 30 percent. You see how important it is for them to have access to checking, to prevention. This study was done in the early 1970's. If we had screened women since then we would have saved 100,000 lives.

The reason so many women do not receive the benefit of new preventive technology is related to their lack of awareness of the benefit of these new procedures. The lack of breast cancer detection and prevention programs in the United States and the lack of private or public insurance coverage for these services is a serious problem—that's where the HMO's are able to provide more medical care than medicare does, in many instances. By providing care, which is primarily a checkup system, they are able to save a lot of expensive stays in hospitals.

Medicare will not pay for most preventive services, like early detection of breast or other cancers. Also, a recent subcommittee survey found that the top 50 insurance companies in the United States do not reimburse women for breast cancer screening tests unless women are symptomatic or have a history of breast cancer in their family, and then it is often too late.

We will hear testimony today that it is possible to do cost-effective breast cancer screening at less than one-quarter of what medicare and most insurance companies pay for similar tests for women who already have symptoms of breast cancer. It will cost about $750 million to screen 30 million women over the age of 45 yearly. This could save 4,500 lives a year. This would equal the cost of three B-1 bombers or eight MX missiles. The cost of each B-1

bomber would save 1,500 lives a year. The cost of each MX missile would save 750 lives per year. If we can afford B-1 bombers and MX missiles, we certainly can afford to save our women's lives.

We will also hear testimony today, that if detected early, breast cancer surgery need not be so radical, and that survival rates can be substantially increased. We must be certain that every woman has the proper diagnosis, treatment, and followup care. We must commit greater resources to basic cancer research.

I remember we started the cancer bill, for a cancer research institute, in 1937. A Senator who had been crippled, named Homer Bones, from Washington, came around to all of us in the Senate with a proposed bill to set up a National Cancer Institute. Well, we had never thought very much about that sort of thing. But he said, "I think we ought to do this, gentlemen," so all of us in the Senate signed a Homer Bones bill to start the National Cancer Institute. That was in 1937.

Well then it provided $500,000 a year for several years. Then that angel of medical mercy, Mrs. Albert Lasker, in New York, came to me in the House, through a former Senator named Matthew Nealy of West Virginia, and she said, "let's start a more effective program for research and meaningful development of cures of cancer, let's appropriate $100 million and have it remain available until it's spent." Not $100 million a year but just appropriate $100 million and have it remain available until spent, because as I said, we were only spending $500,000 a year.

Well, I started hearings in my subcommittee of the Foreign Relations Committee, of which I was the chairman. They ran on for about 6 months and Senator Nealy had hearings on his bill of the same character in the House. Finally Senator Taft, who as you know was a very able, conservative Senator, came and he said, "I think you all are on the right track." He proposed that we appropriate $75 million, I believe, to remain available until spent.

Well, then we got together and we got the first meaningful annual appropriation for cancer and it was about $8 or $9 million a year. The next year we got $14 million and since then, of course, it has gone up until we now have it slightly over $1 billion. And I regret to say that Congress has now become very timid, very fearful, about exceeding, appreciably, that billion dollar limit. They say, "Well, the people have said if we can't find the cure for cancer with a billion dollar fund, why, we can't find it with more money." But I replied to them, "Well, when President Kennedy said we are going to the Moon, he didn't say, 'Provided, we can get there for a billion dollars, I don't want to put more than a billion dollars in it.'"

And when they started to build the terrible nuclear weapon, the atom bomb, in World War II, they didn't say, "Now, we're going to build a nuclear weapon, provided we can build it for a billion dollars. But if we can't build it for a billion dollars we're going to stop right there." They didn't do that for those great projects and they achieved enormous success, technically.

So, it seems to me that we should stand willing to do whatever is necessary. If an enemy were coming into this country and slaying 400,000 of our people every year, I can imagine what would happen to a Member of Congress if he voted against putting all the re-

sources necessary into an effort to stop that monster. But yet I guess we just get accustomed to so many people dying from cancer and we just don't really go after it with determination to succeed. Only 26 percent of the projects that are presented for funding to the National Institutes of Health—projects that have already been rated by the supervisory appellate personnel as being probably meritorious—are funded. Who knows but in those projects that are not funded, there might be the discovery of the cure for that terrible disease.

The small increases in cancer research funds are inadequate for the important tasks ahead. We are fortunate to have with us such a distinguished panel of witnesses, those whose lives have been personally touched by cancer, and expert researchers in this field. This is a significant hearing about a topic that is very important to all of us. We thank you for coming and for giving us support on this worthy topic.

Now my distinguished colleague and friend, Ms. Oakar.

STATEMENT OF REPRESENTATIVE MARY ROSE OAKAR

Ms. OAKAR. Thank you, Mr. Chairman. First of all I think that all women in this country and all people in this country owe you a great debt of gratitude. You are, in my judgment, the most effective Member of Congress that we have, and if you weren't the Chair of this subcommittee I, frankly, doubt that I could have been able to get a hearing on a specific topic like breast cancer, because, unfortunately, it does not seem to be a national priority on the part of many politicians.

I just want to express my very great gratitude to you, Mr. Chairman, and I want to also express in advance my gratitude to the magnificent witnesses that we're going to have today, both people who have contracted that dread disease, and the wonderful scholars who will be testifying as well.

Mr. Chairman, ladies and gentlemen, we're here today to discuss breast cancer, a disease that is the No. 1 killer of women in the Western World. And all women view this, I believe, as the most dreaded disease. The disease is really reaching epidemic proportions in the United States and the National Cancer Institute, American Cancer Society, estimates that there will be 115,000 new cases discovered in our year, probably most of them have already been discovered. There are approximately 1 million women in this country that are living with this dread disease, holding their breaths every time they go for a followup examination to see if their breast cancers have returned since the last checkup.

We have tens of thousands of these women who are suffering from side effects of drugs that they hope are prolonging or even saving their lives.

In spite of all the efforts, and you gave a very interesting historical perspective of how the Institute began, about two-thirds of all breast cancers are found in women covered by medicare and, unfortunately, as you so well know, medicare doesn't cover physicals and all the kinds of things that we need for prevention.

So, we have an estimated 38,000 women who will die of this disease by December 31, 1984.

If we can believe the grim omen of the National Cancer Center for Health Statistics, this year's--and I want to call it what it is, it's an epidemic, that's what it is. That's what breast cancer is, not just any old disease that's out there somewhere. It's an epidemic for women. This raging epidemic will reach national emergency crisis levels during the next two decades. Women who are childless or who do not give birth to their first child until after they're 35 are still, for unknown reasons, at a greater risk of developing breast cancer.

Since 1975, according to the Center's data, the number of first children born to women older than 30 has doubled and there are no signs that the pattern of delayed motherhood will change. If women's patterns do not change, then the patterns of science must change to adapt to this imminent emergency.

I am aware of the fact that the National Cancer Institute has a set a goal of reducing our Nation's death rate from cancer by 50 percent by the year 2000. But what is, and I say this in a spirit of healthy criticism, what is our National Cancer Program doing about cutting the incidence rate? I have studied their budget and am impressed by their proposals and I don't think they have enough money, I want to say that. Here we are in a room where they debate about how much money will be given for military spending, we increased it $200 billion in the last 3 years. So, I want to say that even though my comments are going to relate to what the cancer program is doing, I don't think they have enough resources to do it, and it certainly should be as much a priority as you point out, in licking this disease, as in building more tanks and bombs and giving more aid to countries throughout the world to blow up this universe.

Our attitude ought to be to prolong life, not end it, and it ought to be a priority for this Congress, and the President of the United States.

I'm aware of the great work that they're doing and they have made fantastic discoveries, thanks to the money that we were able to appropriate, and the great research that was done in the last few years regarding the human T-cell leukemia virus and the oncogenes and the other areas that relate to diseases like AIDS and so forth.

But while this detailed overview of the National Cancer Program's activities states that prevention is their top priority, I haven't found a single word about a specific Institute thrust toward finding a way to prevent breast cancer. Indeed, the disease is not even mentioned by name until page 14 of the 45-page document, "Where the disease's unchanged survival rate is 72 percent at 5 years," is mentioned.

Of course, all the research programs will contribute very much toward finding a way to eradicate this disease eventually. But if we're facing what will be an indescribable epidemic, women should not be expected to wait for a byproduct or a fallout from other research to save them from becoming victims of breast cancer.

What I'm trying to say is that we ought to put our focus specifically on cancer and more specifically on breast cancer, because it is a unique form of cancer.

There's one certain method that they tell us will prevent this disease and that's for every women to have a double mastectomy before they even get the disease. I guess that's a black joke and I don't mean it to be serious. But the point of it is that's, I think, the only known way to cure the disease, and that is really ironic, I think, when you think in terms of what the ramifications are.

My interest in breast cancer is personal. My mother, indirectly or directly, died of breast cancer long before she should have. But I doubt that there's a single family in the United States that does not mirror the same concern and the same pain that all of the members of our family went through when my mother was stricken by this dread disease. And so it's not self-serving. I care just as much about people that I have never met who contact this disease, because I understand what they go through when their loved one contacts—and as the Senator knows from his own wife's medical difficulties, this sad, terrible disease. So, we feel strongly on a personal level about this disease.

I want to be sure that there is a treatment available that will destroy the disease the way penicillin destroys bacteria. The National Cancer Institute officials have sat in hearing rooms of both Houses of Congress, have come with their tables, their charts, their graphs, showing how much progress scientists are making with our tax dollars. Most of the time these are identical to the tables, charts, and graphs presented in the 1985 booklet for the Office of Personnel and Management and the budget, National Cancer Program.

While these are impressive and important, and have convinced this Member of the House of Representatives that the NCI is doing excellent work, it's not enough. As a woman, I do not want progress in preventing, detecting, and treating breast cancer to be totally dependent on fallout results from other research. And as a woman who may develop breast cancer, and there isn't a woman in this room that doesn't have that potential, because the incidence is so great, I want this disease to have more research devoted to it exclusively.

I don't think it's asking too much of our scientific community, in an era where our country spends billions every year on defense and space and all the other things that are supposedly national priorities, to say, "Let's really tackle what is within our reach, a cure for cancer."

I do not expect to gets answers to all my questions during this brief hearing today, but I can assure all women, who like me are anxiously waiting for a breakthrough, somewhere, and the 1,400 men who are expected to develop breast cancer in 1984, that there will be more hearings in this Congress about this dread disease that we fear more than any other.

And I will not be content to listen to pleasantries and platitudes invented to keep us happy that progress is being made at a fast rate of speed. I'm delighted that the National Cancer Institute is certain death from cancer will be cut in half by the year 2000. I want the incidence to be slashed as well.

I watch women die of this disease and I'm not satisfied with only a reduction in mortality.

This hearing and those that follow will investigate, among other things, why 12 years and many millions of dollars have left us with the same dismal breast cancer statistic quoted a half a century ago. The statistics are the same.

In addition, I want women to know the areas of prevention, including diet and checkups and self examination. I also want women to understand the options of treatment available at this time. Women should no longer be treated like they are on a man's assemblyline. Women should not have to be drugged, only to wake up without a part of their body. Women should be treated with compassion and sensitivity.

Today I'm introducing a bill that will assure women that physicians and surgeons inform breast cancer patients of alternative, effective, methods of treatment, and will ensure that the woman will have to give her informed consent before any treatment is initiated.

Also, Representative Claude Pepper and myself will jointly introduce another bill which will require medicare to provide coverage for routine cancer screening.

And we're delighted to have these six women who are introducing our panel, who have gone through the psychological pain and the physical pain of deciding which treatment they should have, or worse, the psychological pain they've experienced by not being told of the viable alternatives and given choices as to which one they should be treated for.

Some of these women are free of disease and are cured. Some are members of a group of that million patients I referred to earlier. They're living with breast cancer, worried that it will return. All of them have personal and unique points of view.

In short, Mr. Chairman, I want to see a vaccine for cancer as the major form of prevention, and I think we have the brilliance and the expertise in this country to do it, and I think we have the financial resources to provide those health care and medical experts in research the resources to do it. We've come a little way. Let's go a larger step. Let's make this the No. 1 priority, as we have other No. 1 priorities in this Congress and in the country. And I again want to thank you, Mr. Chairman, for having this hearing and your leadership in this and so many other great issues.

Thank you, Mr. Chairman.

Mr. PEPPER. Thank you, Ms. Oakar, for your excellent statement.

Mr. Andrews?

Mr. ANDREWS. Thank you, Mr. Chairman. I simply am pleased to be associated with the two of you personally and in this most noble effort, and I will look forward to being as supportive as possible.

Mr. PEPPER. Well, we appreciate your interest. We know of your interest in this subject, Mr. Andrews, and the great help that you've given this kind of a campaign in the past, and we are delighted to have your cooperation.

At this time, if there are no objections, I would like to submit the prepared statement of the ranking minority member of this subcommittee for the hearing record. Hearing no objections, the prepared statement of Representative Ralph Regula will appear at this point in the hearing record.

[The prepared statement of Representative Ralph Regula follows:]

PREPARED STATEMENT OF REPRESENTATIVE RALPH REGULA

I thank the distinguished gentleman from Florida for his efforts in calling this hearing on the status of breast cancer in America. This year it is estimated that 37,000 Americans will die from this disease. Yet this figure fails to recognize the larger number who will be maimed emotionally and physically for the remainder of their lives. Eluding the grasp of our sophisticated medical community this persistent killer has maintained its unrelenting stranglehold upon our nation despite the remarkable technological advances of the past two decades.

In 1977 it was calculated that 694,000 years of life were lost in the United States due to breast cancer. Who can measure the true meaning of this loss. Motherless children, careers cut short—breast cancer is an insult and injury to the whole of society.

It is my hope and desire that relief can come to those suffering under this burden. Recent figures show that the approximately 50% of all breast cancers are diagnosed when the disease is localized to the the breast, 41% regional, and in 9% of the cases the disease is already advanced. The probability of survival is directly related to the stage of the disease at the time of diagnosis.

Here, I believe we can strike at the heart of the problem. It is common sense that the greater the emphasis placed upon early detection procedures the more likely we will be able to contain the threat. Educational materials describing self-examination and increased funding for diagnostic research are some example of this "primary prevention" strategy. Unfortunately, efforts to date have failed to noticeably improve the point of detection from that of two decades ago.

As noted in the report preceding this hearing the correlation between diet and cancer may provide another "primary prevention" weapon. The National Cancer Institute is coordinating a pilot study to test the efficacy of a low fat diet (20% calories from fat) compared to the average American diet of 35–40% of calories from fat in inhibiting breast cancer in high risk women. Efforts such as these should be commended.

In regard to the cost reimbursement issue, i.e. DRGs, it is too early to speculate on the effect it will have upon breast cancer therapy. At Senator Dole's request the Department of Health and Human Services met with the cancer research community on April 24th, 1984, to discuss the likely impact of DRGs on cancer research, in particular clinical trials. It appeared to be the consensus that existing data was limited and open to question. It should be noted that the prospective payment system does have a mechanism to monitor and mitigate adverse or unintended effects.

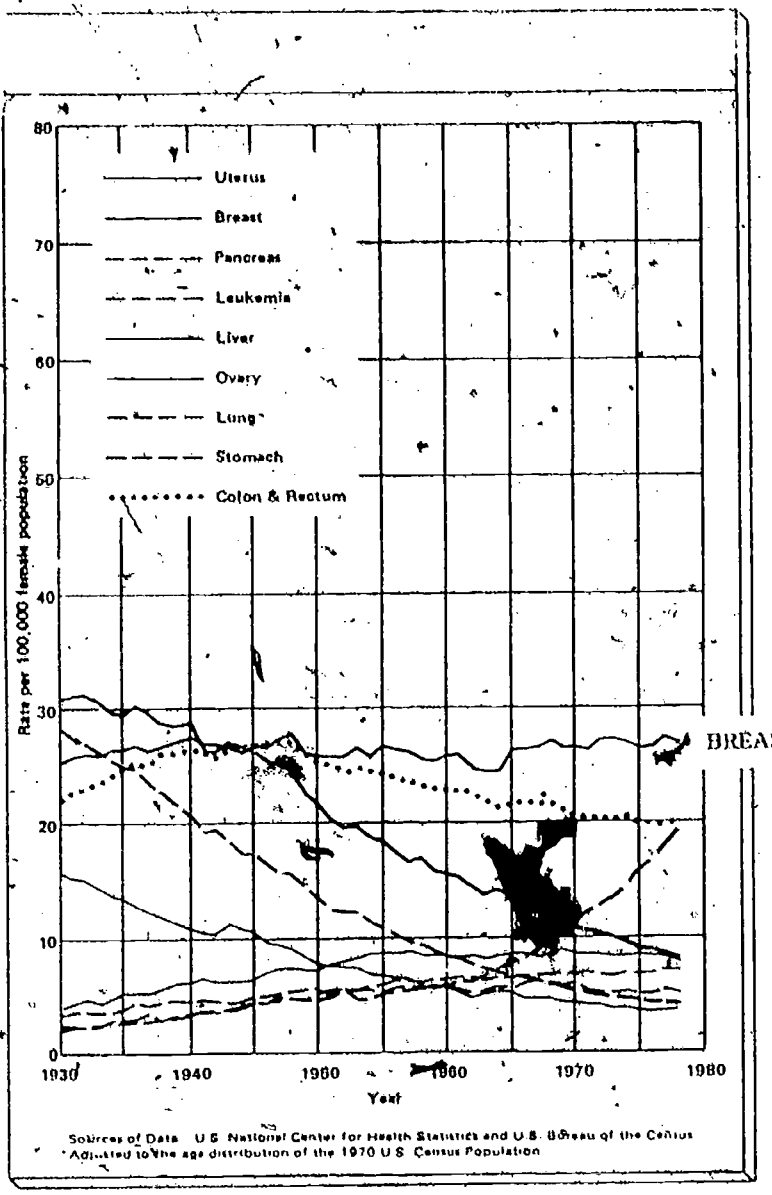
At present, screening and detection services are not reimbursable under Medicare and most third party insurance policies. There are several questions regarding the use of routine screening that complicates the development of a comprehensive reimbursement policy (e.g. what women should be screened and how often). HHS is currently conducting clinical trials on this issue. If the evidence supports the view that Medicare reimbursement for preventive procedures can reduce breast cancer mortality I would support some type of change in the Medicare regulations to effectuate such reimbursement. But to make such a judgement now would be premature due to the insufficient data available.

Again, I would reiterate my appreciation to the Chairman for his concern and assure him of my intentions to do what is necessary to help the victims of breast cancer.

Mr. PEPPER. I would also like to insert a paper entitled "Breast Cancer: An Epidemic in Need for a Solution," for the hearing record at this time.

[The material submitted by Chairman Pepper follows:]

BREAST CANCER:
AN EPIDEMIC IN NEED OF A SOLUTION



A BRIEFING PAPER BY THE HOUSE SELECT COMMITTEE ON AGING
SUBCOMMITTEE ON HEALTH AND LONG-TERM CARE
CLAUDE PEPPER, CHAIRMAN
JUNE 28, 1984

BREAST CANCER: AN EPIDEMIC IN NEED OF A SOLUTION

Approximately seven percent (7%) of women will develop breast cancer during their lifetime. Half of these women will die of or with breast cancer. Breast cancer currently accounts for 20% of all cancer cases among women. There are 115,000 new cases and 37,000 deaths attributed to breast cancer each year in the United States. Probably there are at least 1,500,000 women in the United States who have or had breast cancer. Breast cancer is the leading cause of cancer deaths among women between the ages of 15-74, and second to colon-rectum cancer among those age 75+. Eighteen percent (18%) of all cancer deaths among women are due to cancer of the breast. Unfortunately, in spite of major research advances in diagnoses and treatment, neither the incidence rate -- that is, the number of new cases per year -- nor the death rate (the number of deaths per 100,000 population from breast cancer) have fallen over the past 20 years. This unfortunate fact makes it imperative that a more vigorous and hopefully more effective effort to reduce breast cancer incidence and mortality will occur in the immediate future.

The sheer magnitude of the breast cancer problem can be measured in a variety of ways. In 1980 there were 35,640 breast cancer deaths. Six hundred twenty eight (628) of these deaths occurred among women 15-34 years of age, making breast cancer the leading cause of cancer deaths among these young women. On the other hand, almost a quarter (8,784) of these deaths occurred among women who were 75 or greater, and only colon-rectum cancer accounted for more deaths among older women. In 1983 there were 401,590 cancer deaths among women overall, including 37,000 breast cancer deaths. Breast cancer accounted for 18% of all cancer deaths among women.

Similarly, in 1983 there were 432,500 new cancer cases diagnosed. One hundred fifteen thousand (115,000) due to breast cancer. Thus, 26.3% of all new cases were due to breast cancer.

In 1977 women, breast cancer accounted for 32.2% of all new malignancies in the National Cancer Institute Surveillance Epidemiology and End Results incidence study group women 45-64, and 23.2% for those over the age of 65. Based on data from the 1980 National Center for Health Statistics Hospital Surveys, there were 213,000 hospital admissions overall in which breast cancer was listed as the first diagnosis and 354,000 admissions in which breast cancer was listed on the hospital discharge list. Breast surgery was noted on 365,000 records for both men and women. For these 365,000 records, including the 21,000 men, 3,000 were less than 15 years of age, 169,000 15-44, 120,000 45-64 and 66,000 65+. It is estimated that 3.1 out of every 1,000 women have breast surgery each year in the United States. Furthermore, in 1974 there were 229,000 admissions for breast biopsies and in 1978, 179,000.

A report by Hodgson and Rice on the economic impact of cancer in the United States noted that in 1977 there were approximately 15 million hospital days of medical care for malignant neoplasms in the United States including 2,456,000 for breast cancer, 1,393,000 under the age of 65 and 1,063,000 over the age of 65. The total cost of hospital care for breast cancer based on the number of hospital days in 1977 and the approximate $300 per day minimum estimate for hospital care would equal about $1.2 billion more than the entire budget of the National Cancer Institute. Approximately 200-300 million of those dollars would be for women over the age of 65, most if not all paid from part A of medicare.

Hodgson and Rice also estimated that in 1977 $105 million was spent for physician services including 18% for office visits, 21% for inpatient medical care and 60% for hospital surgical care. Given the fact that physicians' costs have at least doubled since 1977, it is most likely that well over $200 million is spent on physician services for the care of breast cancer patients in the United States each year.

In 1977 breast cancer accounted for 6.8% of the total physician costs for all neoplasms both benign and malignant. Another way of looking at this problem is in terms

of the life-years lost among women who have died of breast cancer. This statistic estimates the number of years a woman would have lived if she had not developed breast cancer and died from it. Overall, on the average, breast cancer robs women of 20 years of their life. For those women over the age of 65, almost 12 years of life expectancy is lost due to breast cancer. Overall in 1977 it was estimated that 694,000 years of life were lost in the United States due to breast cancer. This figure represents 23% of the total life years lost due to cancer, the number one cancer site for women. Current data on the costs to Medicare for the treatment of breast cancer are unknown. Based on the adjusted 1977 data, about $1.1 billion was expended by Medicare in 1984.

There has been a gradual improvement in survival of breast cancer patients among both whites and blacks. Based on data from 1973-1980, the relative five-year survival rate was 74% for white women and 62% for black women. In 1960-63, the same relative five-year survival was only 63% for white and 40% for black women. Thus, survival has improved for both blacks and whites but there still is better survival among whites than blacks. There also seems to be a higher survival rate among the upper as compared to the lower social economic class. The reasons for these differences in survival by race are still not understood. Unfortunately, the five-year survivorship data is a relatively poor measure of the natural history of breast cancer, since a very large number of women who survive five years can be expected to have recurrent disease and many subsequently die from breast cancer. Thus, ten- or even 20-year survivorships are better estimates of the impact of breast cancer.

Survival in breast cancer is directly related to the extent of disease at the time of diagnosis. Disease limited to the breast at the time of diagnosis was associated in the most recent analysis with an 88% five-year survival rate for white and 79% for black women. However, if the disease had spread outside of the breast, usually initially to the lymph nodes in the armpits (axillary nodes), the five-year survival was only 50% for whites and 35% for black women. A more vivid demonstration of the importance of

spread outside of the breast was reported in Cancer: Principles and Practices of Oncology. In Chapter 27, a series of studies comparing ten-year disease-free survivorship was compared by whether there was pathological evidence of spread to the axillary nodes. If the axillary nodes were not involved, ten-year survival was generally around 70-75%. On the other hand, the presence of positive nodes reduced the survival rate to 25 or 35%. Furthermore, the number of positive nodes, 1-3 versus 4 or greater was associated with a further worse prognosis. Women with more than four nodes positive at the time of diagnosis had a 15% ten-year survival or disease-free interval. Even many of these women are most likely to have recurrences of the disease and may subsequently die of advanced breast cancer 15 or 20 years later.

The most recently available figures from 1970-73 showed that only about half of all breast cancers are diagnosed when the disease is localized to the breast, 41% regional and in 9% of the cases the disease is already advanced. Unfortunately, these trends in stage of disease at the time of diagnosis have not improved substantially over time.

What accounts for these rather dismal statistics in the face of major research advances, improvement in treatment and increased expenditures for research and services related to breast cancer? The major factors are threefold. First, the causes of breast cancer are still not fully understood. Therefore, up to the present time, there has been no major effort to prevent the disease, so-called primary prevention. Second, as previously noted, the probability of survival is directly related to the stage of the disease at the time of diagnosis. It is possible to detect the disease at an earlier stage and therefore hopefully reduce the mortality from the disease. Major public health efforts to improve early diagnosis have primarily been limited in the United States to several major research projects and limited health education efforts to increase self-examination of the breast by women, especially those who may be at highest risk of breast cancer. Unfortunately, there is little evidence that the detection of breast cancer is occurring at an earlier stage than it did in previous years. Unless the disease can be detected at an

89-154 O—84——2

ther stage, it is unlikely that the mortality rates will be reduced substantially. Third, it is now realized that breast cancer may be a systemic disease even in its very early stage and that the major emphasis on extensive surgical procedures to remove the breast and surrounding tissues (the so-called Halsted radical mastectomy) may have had little effect on reducing mortality as compared to less radical procedures such as removing the breast alone or even removing the part of the breast containing the tumor (lumpectomy). The combination of any of these procedures furthermore with radiation therapy appears to be beneficial only in reducing localized spread of the disease but has little or no impact on the overall survivorship of the patient. As noted, the five-year survival statistics for breast cancer are very misleading because the disease has a tendency to recur or present itself as advanced disease in other organs years after the initial diagnosis.

In recent years, as will be described subsequently, improvement in drug therapy or adjuvant chemotherapy along with surgical and radiation therapy has helped to improve survivorship and especially to increase the length of time in which the woman is disease-free or able to function in the community. However, it is clear that further adjuvant chemotherapeutic efforts and hormonal therapies are needed and will probably depend on an improved understanding of the biology and natural history of breast cancer.

I. CAUSES AND PRIMARY PREVENTION OF BREAST CANCER

The specific cause of breast cancer is still unknown. However, the many clues currently available may make it possible to substantially reduce the incidence of the disease. The death rate from breast cancer adjusted for age is very high in the United States -- 27.1/100,000. Several other countries also have very high rates, such as Canada (27.8), England/Wales (33.8), and Israel (28.3). On the other extreme, death rates from breast cancer are extremely low among the Japanese 6.0/100,000 less than one quarter of the rate in the United States. Rates were also very low in Puerto Rico (9.2) and in

Yugoslavia, Greece and Poland. Differences in breast cancer rates among these countries correlate best with the amount of fat and perhaps protein in the diet. The differences in the death rates between Japan and the United States or Poland and the United States are not strictly due to genetic factors. Second and third generation Japanese migrants to the United States, specifically to Hawaii and California, have a substantial increase in their breast cancer death rates and incidence, that is number of new cases, so that they begin to approximate those in the United States, white and blacks and are substantially higher than Japanese in Japan. Similar observations have been noted among Polish and Chinese migrants to the United States. These changes in death rates with migration to the United States suggest some new environmental exposure, most likely a dietary factor. Similarly, in Japan the death rates from breast cancer have been increasing and have been correlated both geographically that is by regions of the country and over time with increases and variations in fat consumption in the diet.

Animal experimental studies also suggest a relationship between total fat intake and the risk of breast cancer especially among genetically susceptible animals who are also exposed to selected environmental carcinogens. Recent comparisons of incidence have supported the marked differences in mortality. Rates in Connecticut were substantially higher that from registries in Sweden, Japan, Norway and the German Democratic Republic. These differences in rate of disease among countries is greater for women in the post-menopausal than in the pre-menopausal period. Factors related to a woman's sexual, reproductive and menstrual history are also related to the causes of breast cancer. One of the most important factors related to the risk of breast cancer is age at first birth of a child. Women who have never had a child (nulliparous) are almost at twice the risk of having breast cancer, as women who have had their first child at around age 20. There is a clear inverse relationship between the risk of breast cancer and the age at first birth of a child. Women who have had their first birth of a child over the age of 30 are at even higher risk than women who have never had any children at

all. This phenomenon has been noted in many populations. Thus, a woman who has had her first child after the age of 32 has about three times higher risk of having breast cancer as a woman who has her first child around the age of 20. The risk seems to decrease slightly with increasing number of children. The increasing age at marriage and birth of the first child in the United States could possibly lead to an increase in the number of breast cancer deaths.

The relationship of breastfeeding of a baby to the risk of breast cancer is still a controversial subject. Most studies in the United States suggest that there is either a non-existent or very weak relationship between breastfeeding and breast cancer. An early age at beginning of menstruation (menarche) has been associated with a slight increase in the risk of breast cancer. Increasing intake of calories and better nutrition is associated also with an earlier age of menarche. Women whose natural menopause occurred over the age of 50 have about one and a half times the risk of breast cancer as compared to women whose age at menopause was less than 45.

Surgical removal of the ovaries prior to the time of natural menopause, markedly reduces the risk of subsequent breast cancer. Women who have their ovaries removed prior to age 35 have about one-third the risk of breast cancer as women the same age who have had a subsequent natural menopause. Recent data also suggest that obese women may also have an increased risk of breast cancer especially among post-menopausal women. There is also an increased risk of breast cancer among first-degree relatives of breast cancer patients. The risk is generally greatest if the breast cancer patient is young and especially has bilateral breast cancer. The risk for breast cancer in a first-degree relative of a breast cancer patient is about three times as high if the breast cancer patient is pre-menopausal, and about 1 1/2 times as high if she is post-menopausal. Sisters and mothers of pre-menopausal breast cancer patients who have bilateral disease have almost a ninefold increased risk of breast cancer. About 25-30% of new breast cancer patients have a history of breast cancer in a close relative.

All of these interesting observations in man have been verified by animal experimental studies, including the relationship between fat and total calorie intake, obesity and increased risk of breast cancer. Animal studies have also shown that it is possible to breed high and low risk strains of mice for breast cancer.

There have been numerous attempts in past years to identify a specific viral cause of breast cancer in humans. Certain particles have been identified in breast milk that may be related to a breast cancer virus. Similarly, there have been suggestions that certain environmental chemicals might be related to some cases of breast cancer.

Both humans and animal experimental studies appear to link breast cancer causes with nutrition, hormonal factors, and heredity. Whether modification of the diet especially a reduction of fat and possible weight and obesity) will substantially decrease the risk of breast cancer especially among genetically susceptible women is an extraordinarily important question. Such changes in the diet may hold a key to the successful control of this disease in the United States as well as in other countries. It is important to recognize, however, that there is no proof in humans that is experimental scientific evidence that diethry modification will reduce the risk of breast cancer.

The National Cancer Institute is in the process of planning an initial pilot study to test the efficacy of a relatively low fat (20%) of calories from fat, as compared to the current U.S. diet of about 35-40% of calories from fat in the reduction of the risk of breast cancer among high risk women. It is clear that this type of trial and similar experimental studies in both man and animals must have high pridrity for the prevention of breast cancer. Other nutrients have also been shown to possibly have some relationship to breast cancer. Retinoids a class of compound which includes vitamin A are effective inhibitors of chemically induced cancers in both the mammary gland and the urinary bladder and other sites in experimental animals. Recently modification of the basic chemical structure of the retinoids has produced agents which in experimental animals have increased specificity for breast cancer. Combining treatment with these

retinoids or vitamin A-like substances, and hormone manipulation has resulted in substantial inhibition of the development of chemically induced breast cancer in rats. This combination has also been shown to inhibit the subsequent development of additional breast cancers following surgical removal of the first breast cancer in rats. Retinyl acetate has been shown to be effective in preventing the development of breast cancer after exposure to a variety of chemical carcinogens in these rats. Even if the retinyl acetate is given sometime after exposure to the chemical carcinogen there is a reduction in the subsequent development of breast cancer. The potential use of these agents in both the prevention and as adjuvant chemotherapy for breast cancer is currently under evaluation in several research laboratories. However, it is again important to note that there is no human scientific experimental evidence that any of these agents will prevent or are useful in the treatment of breast cancer.

II. EARLY DETECTION OF BREAST CANCER

Improved survival depends on early detection of breast cancer when the disease is still limited to the breast. A recent study reported that the five-year survival rate was 88% for localized disease, as compared to only 50% if the disease had spread outside of the breast, usually to the axillary lymph nodes. Unfortunately, as noted, only about 48% of new cases are localized at the time of diagnosis. There has been little improvement in the percentage of women detected with early disease during the past 20 years. Most breast cancers are detected initially by the patient as a lump in their breast (90%). Three approaches for the early detection of breast cancer includes self-examination of the breast by the woman, physical examination of the breast by the physician or other health professional and a radiologic technique known as mammography.

To test the efficacy of periodic screening including mammography and clinical examination, the Health Insurance Plan of Greater New York, a health maintenance organization, completed a clinical trial of 31,000 women aged 40-64 who received four

periodic examinations and a similar 31,000 controls who were followed by the usual medical care procedures within the HMO. Initial screening consisted of a physical examination usually by a surgeon and mammography. The screening began in 1963 and ended in 1970. Approximately 65% of the women agreed to the screening procedures. The number of breast cancers found was similar in the two groups. At the end of five years there were 30% less breast cancer deaths in the screened group as compared to the controls and at the end of ten years 24% fewer deaths even though the screening had stopped approximately five years previously. The results of the HIP study suggested that the benefits were greater for older women. During the first five years there were a total of 39 breast cancer deaths in the study group and 63 in the control, under the age of 50 there were 19 in the screened and 20 in the controls, but over the age of 50 there were 20 in the screened and 43 in the control group. After 14 years there were 118 total breast cancer deaths in the screened group and 153 in the control and there was evidence of substantial benefit for both those under the age of 50 and over the age of 50 at the time of the initial screening. Among women whose breast cancer was detected by a mammography the five year survival was 95% and at 12 years 68%. Women in the control group, however, who had positive axillary nodes at the time of diagnosis had only a 27% 12-year survival. No subsequent clinical trials have been done in the United States. A clinical trial has recently been completed in Sweden and new clinical trials are ongoing in Canada and England.

The Breast Cancer Detection Demonstration Project was implemented in the United States to disseminate the techniques of early detection of breast cancer. The project was jointly funded by the American Cancer Society and the National Cancer Institute. There were 29 centers and 280,000 women included in the project, 24,000 (10 %) over age 65. There was no control group as this was demonstration rather than a clinical trial. It is important to note that prior to the study 80% of the women had never had a mammogram and only 36% practiced regular breast self-examination.

Approximately six of 1,000 women were found to have breast cancer at the initial examination and then about 3.5/1,000 new cases each year (incidence) at subsequent examinations. The cancer detection rates were much higher in the older age groups, varying from 1/1,000 age 35-39 at entry to 13/1,000 age 70-74. There were five times as many non-malignant as malignant breast cancers detected. Of the 3,557 breast cancers detected, 1,481 or 42% were found by mammography only, 1,683 (47%) by mammography and physical examination, and 8.7% by physical examination alone. More than 80% of all new cancers among the women were found at the detection centers. Most important, only 20% of the cancers were found to have positive axillary nodes at the time of diagnosis, as compared to the usual of over 50%. No long-term survival statistics from this study have been published. It is also important to note that 782 of the 3,557 breast cancers detected were very small, usually localized cancers, 461 (59%) of these were detected by mammography alone. The study also noted that there were benefits for screening the women under as well as over the age of 50.

Concern about the radiation dose to the breast and subsequent risk of breast cancer had a negative impact on the use of mammography in the early 1970s. In 1976 a report from the National Cancer Institute recommended that mammography not be done routinely for women under the age of 40.

Increased risk of breast cancer were found among women who were irradiated at Hiroshima, Japan, patients treated with radiation therapy for benign breast disease and women who had had multiple chest fluoroscopies for the treatment of tuberculosis. A recent review of this subject in the April 12, 1984 New England Journal of Medicine, noted the substantial reduction in radiation dose from mammography especially as compared to the much higher doses related to risk of breast cancer. They estimated that a modern mammographic study would deliver as low as a 170 mir to the breast and at most could account for perhaps one new breast cancer per one million women screened, as compared to the natural background rate of breast cancer of 1,000/million women.

The study report, however, noted that it is very important to make sure that radiation doses are kept to a minimum and that mammography is done using the best techniques currently available.

The Breast Cancer Detection Demonstration Project also noted two other potential problems. First is the need to do both careful mammography including reading of the film and physical examination to reduce the number of unnecessary subsequent surgical procedures. Thus in the Breast Cancer Detection Demonstration Project the ratio of biopsies performed to cancer detection is about 6-1. Reduction of this ratio without decreasing the number of early breast cancer detected would obviously both reduce the cost and also the number of potentially unnecessary surgical procedures to the women. Another important factor was the need for very careful pathologic examination of the specimens obtained at the breast biopsy. There was considerable concern in earlier studies about the potential for misreading of early breast cancer pathologic changes. Clearly misinterpretation of the pathology could result either in unnecessary breast surgery or the failure to identify an important and essentially curable early lesion.

The results of the H.I.P. study and the Breast Cancer Detection Demonstration project, and other clinical studies in the United States and in Europe, has resulted in revision of the recommended guidelines for mammography and breast cancer detection overall. In August, 1983, the American Cancer Society modified the guidelines it had adopted in 1980, by adding annual or bi-annual mammograms for women age 40-49, to their previous recommendations for annual or bi-annual mammography age 50+. In December of 1983, the National Cancer Institute issued "Backgrounder on Breast Cancer Screening." Major recommendations were: 1) monthly breast self-examination for all women, 2) physical examination of the breast by a physician for all women, for some women it may be yearly for others more or less often. They made no recommendations with regard to a baseline mammogram. Mammography may be considered for women in three high risk categories; a) women age 35+ with a personal history of breast cancer; b)

women age 40 or more with a family history of breast cancer and c) women age 50 or more. "The physician may recommend routine examination with mammography for women not in the three high risk groups because it is very effective in finding early breast cancer," the report stated. These recommendations related to mammography as a screening technique. Mammography may also be an important diagnostic method for any women with a lump or other symptoms.

The American College of Radiology is also now recommending mammography for women under the age of 40 once every one or two years and a reduction of the radiation dose to less than 1 rad. Dr. Myron Moskowitz, Professor of Radiology at the University of Cincinnati and a member of the American College of Radiology Panel noted that at least 7,500 fewer breast cancer deaths/year would occur if all the women had mammograms.

The Health Insurance Plan of Greater New York Study included both mammography and clinical examination. Neither approach alone has been previously tested in a clinical trial. Approximately 85% of all women have had some contact with a physician in the past year. About 50% of women reported having a phsical examination as part of a "check-up" during the past year and another 20% within two years. Similarly 62% of women reported having a breast examination by their physician within the past year and another 20% within two years. These figures should be contrasted with the very low reported frequency of specific preventative breast examinations only 5/1,000 for women age 65+ reported a specific preventive breast cancer examination by their physician.

The frequency with which women have had a screening mammogram is difficult to determine. A 1980 study by Lieberman estimated that only 17% of women over age 50 had ever had a mammogram. A 1979 study by the National Cancer Institute office of Cancer Communication estimated 19% had a mammogram. A 1980 Gallup poll reported a much higher figure; 43%, but again only 14% on a yearly basis. The frequency of examinations, as reported in the Gallup Study is believed to be too high because some of

the women apparently misunderstood the question and believed that chest x-rays included an examination of the breast. It is important to realize that, in spite of the relatively high frequency of reported physicians' visits and examination of the breast, the stage of the disease at the time of diagnosis has not changed and that most, probably close to 90% of breast cancers are detected by the woman herself. The current methods of physical examination by the physician or other health care providers as part of regular medical care does not appear to have a major impact on the early detection of breast cancer and reduction in mortality.

Breast self-examination is believed to be another effective approach to early identification of breast cancer. Mettlin and Cummings reviewed several recent surveys in 1979 and estimated that 94% of women were aware of the techniques of breast self-examination and its importance, but only 40% practiced it monthly. Phillips et al. reported that 30% of Canadian women did breast self-examination monthly. A study in Finland, however, reported that 70% of Finnish women did monthly breast self-examinations. Not only is the frequency of breast self-examination relatively low in the United State but the competence in doing the examinations is also relatively poor. Many studies in recent years have attempted to determine the reasons why women do not comply with monthly self-examinations of the breast and appear to do the procedure inadequately.

A study of 308 women in Baltimore, Maryland reported that 76% performed breast self-examination, but only 39% of those less than 65 and 22% over 65 did monthly examinations. Of the women who performed breast self-examination in the past 12 months, 33% reported that they had received some instruction in how to do breast self-examination from a health professional. The women who did breast self-examination regularly usually were more competent in doing the procedure. The results of these studies suggested that many women perceived the importance of breast self-examination but did not perform the procedure as frequently as necessary, not used proper techniques

in doing the procedure.

Several studies have reported, however that women who performed breast self-examination were more likely to find their breast tumors during the examination than accidental discovery or during routine physical examinations by their physician.

Five studies have looked at the relationship between breast self-examination and the clinical stage of breast cancer at the time of diagnosis. Three studies found that the tumors were smaller among women who practiced breast self-examination but two studies found no differences.

Other studies have attempted to evaluate the characteristics of women who performed breast self-examination. Most studies have determined that women who are better educated, upper income and younger married women are more likely to perform breast self-examination. Instruction in breast self-examination by a health professional was also an important determinant of the frequency and quality of the breast self-examinations. Also a history of breast cancer in the family was associated with an increased frequency and competency in doing breast self-examination.

Thus, most women appear to understand the importance of early detection of breast cancer, and the need for breast cancer, and the need for breast self-examination. However, fewer perform the monthly examinations, many do it poorly, are inadequately trained by a professional in the methods of self-examination and there is little followup to determine how successful the women are in performing the procedure. The value of breast self-examination in reducing mortality by identifying lesions at an earlier stage remains a belief rather than a proven scientific fact. It is reasonable to presume however that the addition of breast self-examination to an early detection program will enhance early detection and hopefully reduce mortality. It is clear that the current health education programs are inadequate and that more vigorous health education including the training of the women in breast self-examination, the importance of continuing to do the procedure and followup of the women is necessary if breast self-

examination is to be utilized as an effective approach to early detection and reduction of mortality.

There have been no community-based breast cancer prevention programs in the United States. A study in Holland is the closest example of a community based effort (Diagnostic Investigation of Breast Cancer). The project involved screening of women aged 50-64 for breast cancer including mammography and physical examination and a nutrition program oriented primarily toward weight reduction.

The study began in 1974. Women in the City of Utrecht, aged 50-64, were offered four screening examinations. The first two within 12 months, the next 18 months and the last 24 months apart. Paramedical personnel were trained to both take the mammograms and to do the initial readings. They also did the clinical examinations. Each woman was asked to contribute $5.00 to the cost of the examination. Radiation doses were relatively low, only 0.4 rads. per examination. National background radiation is about 0.2 rads. per year and a chest x-ray is estimated to contribute about .04 rads. to the chest.

The response rate of the initial screening was 72% for the eligible women and the followup examination about 80%. Invitations to participate had been sent to 20,355 women. Between 1974 and 1980, a total of 61,649 breast examinations including mammography were performed. Preliminary results of this important study have recently been published. An abnormality on the basis of combined clinical and mammographic investigation, suspicious of breast cancer resulted in a recommendation for biopsy in 263 (1.8%) of the women, 201 (1.4%) had a suspicious finding requiring followup, 252 a lump in the breast which appeared to be benign, 13,981 (95%) of the women were found to be normal. Of the 263 with a suspicious lesion, 101 (38.4%) had a malignant lesion and 152 (57.8%) benign and in 10 (3.8%) women refused the biopsy. Of the 198 cancer detected, 138 (70%) had negative axillary nodes at the time of diagnosis including 89 (82%) of the 109 detected by mammography only and 49 (56%) by clinical examination and mammography. These results contrast very favorably with previous

observations that less than 30% of patients with breast cancer have negative axillary nodes at the usual time of diagnosis either in the United States or in Holland. A further important observation is that the new cases detected later in the study after the first year usually had negative axillary node. These are the incidence cases, the ones that would be most important in detecting in any long-term community based prevention program. Cancer detected through the screening program were also smaller than those detected in the same population prior to the screening process. Ninety-five percent (95%) of the cancers that occur within 12 months of any examination were detected by the screening examination, the remaining 5% by the woman herself. Only 8 of 210 cancers detected by the screening were found solely on the bases of clinical examination without mammography. Followup including survivorship of this important population is continuing.

Recently an initial evaluation of this study was published in the June 2, 1984 issue of "Lancet". The authors stated that "the risk of dying of breast cancer among women screened was 30% of that of women never screened. Longer follow up, however, is still necessary. A similar study from Nijmegen, Holland pulished in the same issue stated that the risk of dying of Breast Cancer among women screened had been reduced by 50%.

The initial results of this study have very important implications for the prevention of breast cancer in the United States. First, women can be recruited into a breast cancer prevention program (72% of those eligible). Second, paramedical personnel can be trained to do and read mammograms in a community based prevention program substantially reducing the cost with little evidence of a major reduction in sensitivity of the procedure. Third, mammography has again been demonstrated to be able to identify small, localized breast cancers which might be associated with substantial decrease in mortality. Fourth, a careful, well-organized followup is possible and can be done successfully.

It is also clear that given the yield, 7.3/1,000 breast cancers at the initial screen

for prevalence) and 2.1/1,000 subsequently (incidence) a cost-effective method for screening is necessary. At $150 a mammogram a fairly standard price in the United States, the screening of these 20,000 women during the first year alone would be over $3,000,000 and yield 110 breast cancers or about $21,500 per case just for case finding. It would be financially impossible under the current procedures to screen the eligible United States population of perhaps over 40,000,000 women. A public health or community health effort, such as the Dutch Project, will be required. As noted in the American College of Radiology Report, community based cancer detection centers both to improve the quality and reduce the cost of mammograms and follow-up will be necessary. At present, there are few such programs in the United States, the stage of disease at the time of diagnosis has remained unchanged over time as has both the incidence and breast cancer death rates. If the 30% reduction in mortality noted in the HIP screening study has been applied to the United States population subsequently there would be at least 7,000 lives saved each year in the United States. If these procedures has been in place since the initial results of the HIP study in the early 1970s there probably would have been a savings of almost 70,000 lives. Without any organized community based program there is little likelihood that there will be a substantial reduction in breast cancer mortality in the foreseeable future in the United States. The program at the Guttmann clinic in New York and Florida has substantially reduced the cost of screening to the current cost of $35. Over 10,000 women have been screened in Florida at the Center. Newer imaging techniques such as Nuclear Magnetic Resonance may enhance the early detection of breast cancer. The continued failure to implement early detection programs will have an adverse effect on the health of American women.

III. Breast Cancer Treatment

Major changes in the treatment of breast cancer are continuing and include modification of surgical procedures, use of added chemotherapy and hormones (adjuvant)

therapy and radiation, as well as new techniques of rehabilitation and psychological support. Until the 1970's there was relatively little controversy as to how breast cancer should be treated especially if the woman had no evidence of spread beyond the local area. The woman was subjected to a radical mastectomy and might also receive radiation therapy. The initial surgical approach was based on Halsted, a famous surgeon of the early 1900's concept of the spread of breast cancer. As discussed by Fisher, et al, Halsted believed that extension of the cancer from the primary site was by direct spread, called permeation. The concept of the spread of the cancer was the basis of the radical mastectomy.

In the 1930's and later it became clear that passage of tumor cells in the blood stream (embolization) is the predominant mode of spread to the draining lymph nodes and to distant sites. Furthermore, it was originally thought that spread of breast cancer was sequential from breast to lymph nodes to distant sites. More recent work, however, suggests that spread to draining lymph nodes and to distant sites may occur independently although they are highly correlated processes. The presence of a tumor in the axillary nodes at the time of diagnosis is a bad prognostic sign, but not necessarily the cause of the bad result. Further studies have also suggested that there may be important host-defense mechanisms that are capable of eradicating untreated tumors and that these untreated axillary lymph node growths do not necessarily serve as a focus for future spread of breast cancer. Some investigators have suggested that treatment of draining lymph nodes may in fact be harmful.

The value of the specific types of breast cancer surgery and radiation therapy have been evaluated in several important clinical trials. The results of these clinical trials were that:

1. In the United Kingdom in 1970, compared simple mastectomy plus radiation to simple mastectomy alone. There was no difference in survival in the two groups. Although patients receiving radiation therapy had fewer local

recurrences. Similar type studies in Britain have had the same results.

2. In 1971 a trial was begun in the United States by the National Surgical Adjuvant Breast Cancer Project (NSABP) that compared simple mastectomy, radical mastectomy and simple mastectomy and radiation therapy. Again localized and regional recurrences were reduced by radiation therapy but there were no differences in survival among the three treatment groups. A five-year relapse free of breast cancer, survival was 71% for simple mastectomy and radiation, 63% for simple mastectomy alone and 68% for radical mastectomy. Fisher noted these studies suggested that treatment of axillary nodes is neither harmful nor beneficial with regard to survival.

The newest approach to breast cancer surgery is segmental mastectomy, partial mastectomy or lumpectomy. All of these are essentially the same procedure. Many initial reports have been very favorable. A clinical trial by the NSABP has recently been completed and should be published shortly. This approach, however, has been primarily limited to women who have relatively small tumors and can expect a good cosmetic result.

A combination of early detection by mammography and subsequent segmental resection may offer a very promising approach to both saving lives and providing a safe and the best cosmetic approach, preserving most of the breast tissue. However, until the results of the clinical trials of segmental mastectomy are published and critically reviewed, the procedure should still be considered experimental. Other trials of segmental resection were started in 1978 in Italy and in the United Kingdom. The preliminary results of the Italian study have recently been published. The study was limited to patients who had small lesions less than 2 cm without clinical axillary node tumors. Surgery consisted of removal of the quadrant of the breast with the tumor plus

dissection of the axillary nodes and radiation therapy. Such patients have had similar survival as patients treated with radical mastectomy. The United Kingdom studies initially show no differences in the survival at ten years between segmental resection and more extensive surgery among women with negative axillary nodes.

The results of the clinical trials have had a major impact on the treatment of breast cancer. The 1982 long-term survey by the American College of Surgeons (ACS Bulletin, September, 1983), noted that 55% of the patients treated in 1976 had undergone a modified radical mastectomy and 28% a radical operation. The 1981 audit showed that 3% of women in 1981 had received a radical procedure while 78% had undergone a modified technique. The 1982 survey showed that 7% of women had a segmental procedure as compared to 3% in 1976. Furthermore, more detailed analysis of the overall trends noted that radical procedures had declined from 40% in 1972 to 21% in 1977 to 4.5% in 1982. These figures indicate the end of more than a half century of standardized treatment by radical mastectomy and represent a major advance in surgical therapy for the treatment of breast cancer.

The era of taking a patient with unproven diagnosis of breast cancer to the operating room, performing a biopsy and frozen section for pathological examination during anesthesia and then a definitive operative procedure, the so called one-stage approach, including subsequent mastectomy has also come to an end.

Now when a mass is detected in the breast the diagnosis may be established by one of three procedures, all on an out-patient basis and generally under local anesthesia.

1. Analysis of cells removed by needle aspiration of the breast.
2. Removal of a core of tissue (biopsy) and subsequent pathological examination.
3. An excisional biopsy, that is removal of the entire tumor, may also be done if the tumor is relatively small.

It is extremely important in all of these instances that excellent pathology

facilities is readily available. Receptors for specific sex hormones, estrogen and progesterone are found on the surface of these cells. The subsequent course of disease and specific follow up, chemotherapy and possibly hormonal manipulation depends on the presence or absence of these hormonal receptors. Thus, good surgical care now requires: 1) proven diagnosis prior to definitive surgery, including evaluation of receptor status, 2) the best type of surgical procedure most likely to preserve the maximum amount of breast tissue with or without subsequent radiation therapy, and careful followup of the patient including the needs for adjuvant chemotherapy.

These are extremely important areas for professional education of the surgeon and other physicians, as well as careful monitoring of the trends in breast surgery and after care. Programs have been developed by both the American College of Surgeons and the National Cancer Institute. It is also important to educate women about the various types of diagnostic and subsequent surgical procedures and the importance of their contribution to their own care.

Systemic therapy of breast cancer with anticancer drugs and hormone therapy has also changed during the past 10-15 years. A report from the American College of Surgery, noted that there was a substantial increase in chemotherapy following surgery from 12-16% over a five year period, between 1976-1981. Also only 3% of patients with advanced regional disease had received chemotherapy in 1972 as compared to over 35% in 1981. Radiation therapy is also beginning to become less frequent. In 1972, 45% of patients received radiation therapy, while in 1981 only 13% received such therapy. The use of combined surgery, radiation and chemotherapy in the treatment of breast cancer was recently reviewed by the Council on Scientific Affairs of the American Medical Association (JAMA, May 11, 1984).

The American Medical Association report noted that "controlled clinical trials have established the value of chemotherapy in patients who develop breast cancer prior to their natural menopause and who have positive axillary nodes." The relapse free survival

at five years is improved from 15% in controls to 60% in treated patients. A combination of chemotherapeutic agents appear preferable in most studies.

In post-menopausal women with positive axillary nodes, the role of added (adjuvant) chemotherapy is more controversial. The various clinical trials have had conflicting results.

Early trial of hormonal manipulation as adjuvant therapy of primary breast cancer included the removal of the ovaries in patients prior to the menopause. The results of a major trial in the United States were essentially negative. A more recent Canadian trial reported significant benefit however, 53% versus 29% disease free at ten years. These treatments however were all conducted before the discovery of estrogen receptors.

Recently an antiestrogen drug (tamoxifen) has been combined with chemotherapy in post-menopausal women who have estrogen receptor positive lesions. Treatment with tamoxifen prior to menopause who have estrogen negative tumors may however have an adverse effect. A more detailed review of the Impact of Randomized Clinical Trials on the Therapy of Breast Cancer, the NSABP overview was recently published in controlled clinical trials, 1982;3:209-225.

The most recent randomized trial of a combination of chemotherapeutic drugs and hormone therapy with taxoxifen was reported from Europe by the Ludwig Breast Cancer Study Group in the June 9, 1984 Lancet. At a median followup of 36 months, disease-free survival was significantly greater in women receiving the combined treatment as compared to taxoxifen alone or controls. Unfortunately there was no improvement in life expectancy by the treatments. The authors concluded that endocrine therapy reduced local and regional recurrence only.

Probably one of the most important advances in cancer research has been the identification of specific human cancer genes called oncogenes. The importance of oncogenes in relation to breast cancer was recently reviewed by Dr. William Feller of Georgetown University Medical School at a June 6th Hearing of the Subcommittee on

investigation and Oversight of the Committee on Science and Technology of U.S. House of Representatives. Dr. Feller stated, "It is likely that the breakthrough on oncogenes will open several new strategies for cancer diagnosis and treatment within the next decade." Preliminary work in Dr. Feller's laboratory has resulted in a possible blood test for early breast cancer detection. Furthermore, the understanding of oncogenes may result in new types of therapy. "Can we devise strategies to switch off cancer genes."

The identification of specific genes or their products could then head to development of antibodies, such as against viruses or bacteria that could identify and destroy the tumor. Such new "immunotherapy" may improve diagnosis and treatment.

The question as to whether breast cancer is really curable remains a controversial subject. As noted late recurrences and death from the disease are not infrequent. A recent report of 14,731 cases of breast cancer from the Cancer Registry in Norway with an average of 5-18 years of followup, noted that perhaps 33% of breast cancer patients were cured. A model was developed to estimate this cure rate, defined as women with previous breast cancer who now have the same risk of death from all causes including breast cancer as women without the disease. The cancers were also classified by stage of disease (Cancer, April 15, 1984). Stage I localized with no axillary tumors, II localized with tumor outside the breast, to stage IV advanced disease at time of diagnosis. The cured percentage with up to 15 years of followup was 54% in stage I, 27% in stage II, 10% in stage III, and only 2% in stage IV. The median survival of the non-cured patients in stages II,III, and IV was less than five years. Late mortality from breast cancer occurred frequently even after five or even ten years of inactive disease.

A similar recent letter to the editors of the British Journal Lancet reviewed the experiences in the Cambridge area after a 22 year followup. Even after 20 years of followup there were still 13 times as many breast cancer deaths as expected. However only 26 of the 704 patients (3%) had developed breast cancer in the opposite breast over the 30 year followup. Adair in a 30 year followup of patients treated at Memorial

Hospital in New York estimated only a 21% cure rate.

The conclusions of the Lancet article were "thus long-term studies now suggest that statistical cure (i.e., the attainment of a group subject only to normal mortality risks) has not yet been demonstrated in breast cancer. However, a significant proportion of patients will experience "personal cure" in that they live without overt signs of their breast cancer until they die from some other cause. In our series, 176 (26%) of the 683 deaths fell into this category."

The implications of these findings are many fold. First the treatment of breast cancer requires continued basic research and careful testing in clinical trials. We are still a long way from a combined surgical, radiation and medical therapy for curing breast cancer. The use of chemotherapy is not a witch's brew to be used without careful planning, followup and most important use of scientifically tested protocols. The recent articles in the New England Journal of Medicine described the problems of recruitment of subjects into these clinical trials especially for breast cancer. Better education for both the physicians and the patients about the great importance of a systematic approach to treatment is necessary. It is extremely unlikely that further advances in reducing mortality will continue without a combination of careful basic research to identify new therapeutic modalities and long-term clinical trials.

Second, the introduction of the DRG system may have a substantial adverse effect on the quality of breast cancer therapy by restricting the frequency of diagnostic procedures and the admissions of patients to specific protocols as part of clinical trials that may be more costly than conventional, but perhaps less effective therapy.

Third, the competition for patients at the lowest possible cost may drive patients from major cancer centers and tertiary care hospitals which have higher costs to less expensive institutions in the community. Most cancer patients can probably be treated in community hospitals and major teaching and tertiary care facilities are required if therapeutic efforts are to continue to improve. The National Cancer Institute has been

attempting to develop such bridges. However, recent changes in the Health Care Financing System may provide obstacles to the continued development of these outreach programs and especially the development of systematic treatment protocols as part of clinical trials in community hospitals. A dollar saved may be a very costly dollar in terms of the health of the women.

Fourth, better health education of women is necessary especially in relationship to the early diagnosis and the alternative forms of specific therapy. Most important, women who have localized, small lesions, may probably be treated by segmental resection or lumpectomy. The morbidity after such surgery is minimal and various rehabilitation procedures including reconstruction surgery are currently available. Neither social nor sexual relationships need to be abnormal after any of the surgical procedures. A recent article in the Lancet (February 25, 1984) has reviewed this subject.

Finally, in order to reduce the mortality from breast cancer, a vigorous four-pronged effort is clearly required:

1. There is a major need to test methods of primary prevention of breast cancer, most likely by nutritional modification. The years of both basic animal research and human epidemiological and clinical studies must now be tested by careful clinical trials to determine whether low-fat diets, calorie restriction and weight reduction or other chemoprevention agents, such as vitamin A and other retinoids will reduce the incidence, or number of new cases of breast cancer. The evidence that such nutritional approaches will reduce the incidence of breast cancer is currently circumstantial and requires careful clinical trials for validation. Modification of the diet of the United States population to prevent breast cancer by reducing fat intake would have a major effect on certain industries in the United States. A clinical trial of this approach should be done prior to the generalizability of this effort.

2. A community based effort to increase early detection of breast cancer by mammography, physical examination, and breast self-examination by women and possibly newer diagnostic techniques must be developed. The current cost of mammography and clinical examination makes a national effort toward breast cancer prevention unlikely without a substantial use of health care resources. On the other hand, there is no reason why less expensive and equally effective community-based programs cannot be developed especially with the use of paramedical personnel and newer, less costly screening technology.

3. A continued effort in basic research and expansion of clinical trials to identify better methods of treatment especially of advanced disease is critically important. In spite of our efforts in chemotherapy and radiation therapy and hormonal manipulation the results of the treatment of women who have axillary node involvement at the time of diagnosis or other advanced disease is still dismal, and an aggressive effort in development of new treatment modalities is clearly necessary.

4. Continued active research to identify the specific cause or causes of breast cancer is still top priority. However, we have learned a great deal about the specific environmental and certain genetic factors related to breast cancer, and continued basic research should not reduce or eliminate the need for careful clinical trials and evaluation of the important leads of the research from the past 10 or 20 years.

Mr. PEPPER. Now we will proceed with our first panel of witnesses. We have an excellent panel, consisting of Mrs. Irene Cohen of Deerfield Beach, FL. Then we will hear from Mrs. Doris E. Levin of Rockville, MD, Mrs. Ruth Spear of New York City, Mrs. Janet Nixon of Chicago, IL, Mrs. Carolyn Alford of Midlothian, VA, and Mrs. Rose Kushner of Kensington, MD. We are delighted to have you ladies here, and would like for you, Mrs. Cohen to lead off, please.

PANEL ONE: CONSISTING OF IRENE COHEN, DEERFIELD BEACH, FL; DORIS E. LEVIN, ROCKVILLE, MD; RUTH SPEAR, NEW YORK, NY; JANET NIXON, CHICAGO, IL; CAROLYN ALFORD, MIDLOTHIAN, VA; AND ROSE KUSHNER, KENSINGTON, MD

STATEMENT OF IRENE COHEN

Mrs. COHEN. My name is Irene Cohen. I am 76 years old and live in Deerfield Beach, FL. If it was not for the Breast Cancer Screening Clinic, I would not be alive today. I volunteered for cancer care, a group that helps cancer patients. At a meeting in October 1980, a speaker from the new Breast and Cancer Detection Center came to our meeting. On December 11, 1980, I went to the screening center and had a mammogram. I was completely normal and had not felt a lump or had any suspicion of breast cancer. On December 18, only 7 days later, I was advised that I had an abnormality in my right breast. I went to a surgeon on January 1, 1981, was diagnosed as having breast cancer, and on January 22, 1981 had a right modified mastectomy. I go back to the clinic every 6 months for a checkup. During the past 3½ years since the diagnosis, I have had no recurrence of the breast cancer. I did not need radiation therapy or drug therapy, chemotherapy. The screening examination at the center saved my life by finding the breast cancer while I was still curable.

I wrote an article called "My Lucky Day" for our local newspaper. A copy of the article is available for the committee. I believe that prevention centers such as the Breast Cancer Detection Center are very important, especially for our older citizens. I am healthy and active now because I have participated in preventive programs since the beginning of 1950 in New York City sponsored by the health department and Memorial Hospital.

I believe that it is very important that all citizens be aware of the importance of preventive health programs. Centers such as the Breast Cancer Detection Center should be established all over the country and all individuals, especially older citizens, should be urged to participate. Based on my personal experience, I am certain that this will save lives like my own, make the older years more pleasant and enjoyable and save millions of dollars for the Government by reducing expensive health care costs for treating severe diseases.

I want to read my report called "My Lucky Day." Ladies of all ages, take a few minutes to read this letter. If you do, you will benefit from it. It may extend your days and even save your life, as it did mine.

On October, 1980 I went to a meeting for cancer care for the homebound at the Chamber of Commerce in Deerfield Beach, FL.

A speaker came to tell us that the Philip Strax Breast Cancer Detection Institute was planning to open a breast clinic in Florida, as they felt there was a great need for more information about breast cancer. I said to the group of women, "Let's sign up for the check-up." After some pros and cons, four of us did sign up.

On December 11, 1980, we all went to the Philip Strax Breast Cancer Detection Institute at 5975 West Sunrise Boulevard, Suite 203, Fort Lauderdale.

We were examined by a certified doctor and then had a mammogram taken. There is nothing demeaning in such an examination. There is nothing to be afraid of. It cannot harm you.

On December 18, 1980, I and three other ladies of our group were recalled for a reexamination. I was the only one who had a real problem. After Dr. Philip Strax examined me, he told me I should have an operation but suggested that I go to another doctor of my choice for another opinion, and then make up my mind. I went to two more doctors, both of whom agreed that I needed the operation.

On January 20, 1981, I was operated for a modified mastectomy. When I was alerted that I had the problem, which turned out to be cancer, I did not waste any precious time. I faced the facts with open eyes and acted fast for it could save my life and perhaps avoid years of untold suffering and treatment.

My mental attitude and my determination that I was going to get well helped me. I got right back into the swing of housework, shopping, and social activities.

This much I can say: If I hadn't heard about the Philip Strax Breast Cancer Detection Institute and followed up on the tests and mammogram, I might not be enjoying good health and a clear mind today, I hope for many more years ahead of me.

This story is told from the depth of my heart, hoping its message will show women the importance of regular breast examination. Some women may someday say, "It was my lucky day when I went to Philip Strax Breast Cancer Detection Institute for an examination."

Mr. PEPPER. Mrs. Cohen, that's a very compelling statement. We appreciate very much your coming to make it.

Mrs. COHEN. Thank you very much.

Mr. PEPPER. Now, the next is Mrs. Doris E. Levin of Rockville, MD.

STATEMENT OF DORIS E. LEVIN

Mrs. LEVIN. Members of the subcommittee, ladies and gentlemen, my name is Doris E. Levin and I'm from Rockville, MD. Almost 5 years ago I went to a doctor because I had a suspicious lump in my breast. He aspirated or removed fluid from the lump, and did not send the fluid on to a lab for further analysis. About 1 year later I visited the Georgetown Hospital Breast Cancer Clinic. I had for some time participated in the clinic's early breast cancer detection program, wherein I would be followed for 5 years in order to detect cancer in its earliest stages.

To my surprise, Dr. William Feller, who is the Director of the Center at Georgetown Hospital, took one look at my breast and

said, "You look like you have breast cancer." I, in fact, did have breast cancer and Dr. Feller performed a modified mastectomy.

I would not be here today had it not been for the Breast Cancer Clinic. I am one of the lucky ones. Had I not enrolled in this voluntary breast cancer screening clinic, I would never have known that I had breast cancer. It was not until after I had discovered I had breast cancer that I learned how important it is to detect such cancers at an early stage.

With early detection, a woman's breast can be saved, her life can be saved. Unfortunately, most women wait until symptoms express themselves, like mine did, and the prospects for survival are substantially reduced.

Following my breast surgery, I began working with voluntary organizations involved with helping other women with breast cancer. As a result of this activity, I found that women, especially women in rural areas, simply don't have the services and opportunities for routine exams for breast cancer, such as I had.

Breast detection centers should be made available to women throughout the United States.

I also found that many older women are generally not able to look to public and private health benefits programs to help them pay for such preventive screening. For women over the age of 65, many of whom are living on one-half of the income of those who still are working, they simply don't have the discretionary income. Most public and private insurance pays only when a woman is suspected of having cancer, and that is often too late. It is unfortunate that the breast cancer detection program, such as at Georgetown Hospital, is no longer financially supported by the American Cancer Society or National Cancer Institute, and that such centers are not available in every community in the United States.

Last, I just want to say again that I would not be alive today if it weren't for the good work begun at the breast cancer clinic under the direction of Dr. Feller. I only hope that my testimony will serve only to continue their work and to provide breast cancer clinics.

Dr. Feller's dedication and devotion to this cause should make it possible for this worthwhile program to be continued.

Thank you.

Mr. PEPPER. Well, thank you very much for your excellent statement, Mrs. Levin.

The next is Mrs. Ruth Spear.

STATEMENT OF RUTH SPEAR

Mrs. SPEAR. Chairman Pepper and members of the committee, there is no contemporary disease that you can name that a greater number of people, namely women, spend more time thinking about and fearing than breast cancer. If every woman does nothing more than the monthly breast self examination that the American Cancer Society advises, that's a minimum of 12 times a year that she thinks about it. And more often than not this examination is avoided altogether, exactly because what it might reveal is so feared, a lump that, if malignant, means an immediate mastectomy at the very least, and death in a good number of cases.

Breast cancer, though epidemic among American women, is a disease about which they are told very little until they contract it. A shockingly high number of women are not informed that they have a right to demand a two-step surgical procedure. Fewer are told about new treatment options. And rarely is prevention mentioned.

Two-and-a-half years ago I discovered a small lump in my right breast during my monthly self examination. It showed as a tiny speck on a mammogram. I was told by a breast specialist that if it proved malignant on biopsy and if I cared a great deal about the way I looked, it was possible to have the lump removed and have radiation therapy. But if I cared about living a long time, I would have a mastectomy.

Frankly, I cared about both. I felt that this major decision should be made neither on the basis of vanity or fear, but rather, on whether I qualified medically for a viable alternative among the newer, less-devastating treatments that I had been reading about.

Obtaining information was very difficult. I was extremely fortunate that, being a writer, the journalistic pipeline made information available to me that simply would not easily be within the reach of the average woman. And at a time of trauma like hearing you have breast cancer, I doubt that the average woman would be cool enough to seek it.

I learned that several European studies had shown that 10-year survival rates for women with early breast cancer that had not spread to the adjacent lymph nodes and who received the lesser treatments were virtually the same as for those who had mastectomies. I learned about myself that the small size and location of my lump made me a good candidate for lumpectomy and radiation.

But I really had to shop around to find the best place to do this and I had to close my ears to a lot of scare talk from some doctors who simply were not well informed about the latest techniques.

My treatment took place at Memorial Sloan Kettering Cancer Center in New York. At that time, only 2½ years ago, the availability of such treatment at a surgically oriented hospital was sort of a well-kept secret, discouraged by most breast specialists who, being surgeons, have a built-in bias. I am happy to say that at Memorial and at other major teaching hospitals, this has changed dramatically in the last 2 years, as more and more doctors learn about the new modalities.

But this still applies only to select urban areas.

There's a great deal more that can be done and in the forefront is education. Within a short time after my treatment, I found myself receiving telephone calls from women all over the country who heard about my treatment from a friend or relative or neighbor. To these women, women's networking seemed the only way that they could get information. Now, there's something wrong with a system where women have to go to other women for information they should be getting from a doctor or a specialist, or a specialized agency.

When I subsequently wrote a detailed account of my experience, along with basic information on breast cancer in New York Magazine, the response in letters and telephone calls was double that

usually elicited by stories in the magazine, another barometer of how hungry women are for this kind of information.

It's time for the Government to recognize the various areas of work that must be done to reduce the mortality and morbidity of breast cancer in this country. Any woman with a close female relative who has had breast cancer is at higher than average risk, and the average risk is already high.

I would like to see more research done on the hereditary implications of breast cancer, so that some preventative modality could be formulated. And speaking of prevention, I feel fortunate to know about the link between dietary fats and breast cancer, and to have had the opportunity to become part of Dr. Winder's low fat program.

But I am saddened when I think that the opportunities I had do not exist for the 1 out of 11 of my sister Americans across the country who will develop breast cancer at some time in her life.

It should be a national priority that women be educated both in their rights and in the new techniques of prevention, detection, and treatment. A State law requiring that a woman needing a breast biopsy be informed of her right to a 2-step procedure such as was first enacted in the State of California, is a step in the right direction. But it needs supplementation.

California also has a brochure explaining not only the rights but all the efficacious and viable treatments available for breast cancer. But many women do not understand what they read.

What is also needed is that each State provide a breast disease specialist, a sort of breast cancer ombudsperson, if you will, an official someone, a person, or an agency, available to interpret the facts to anxious women. We like to think that doctors will do it, and they should do it, but the fact is they don't have the time, and they often don't have the inclination.

The national Government must make each State understand that simply having a law and having a brochure is not enough.

The prevention of breast cancer through dietary modifcations is an exciting concept that promises much and needs the support of the food industry, the medical establishment, as well as the appropriate Government agencies. Low dose mammography should be available to all women, regardless of economic status, and not merely to confirm clinical findings, but as an early screening device.

The benefits of low dose mammography far outweigh the risk, which is a fact that must be publicized among women. Women need to learn that looking for trouble is the best way to avoid it, which brings us right back to education. A woman is much more likely to examine herself regularly and report suspicious findings promptly if she knows that a lump, if malignant, does not automatically mean a mastectomy. And she needs to know that if a mastectomy is ultimately necessary, that reconstruction is available to her.

I am informed that this subcommittee has drafted legislation like Ms. Oakar's no surprise bill, and Mr. Pepper's bill which we heard about this morning, to make mammograms as available as chest x rays. So, I urge you on behalf of the women of this country to act favorably upon them and to support any other legislation that will

help fight the disease from which 38,000 American women will die this year.

Thank you.

Mr. PEPPER. Thank you very much, Mrs. Spear; for your very fine statement.

[The prepared statement of Mrs. Spear follows:]

PREPARED STATEMENT OF RUTH SPEAR, MANHATTAN, NY

Chairman Pepper and members of the committee. My name is Ruth Spear and I am a breast cancer patient. In early November 1981, I discovered a small lump in my right breast when I did my monthly self-breast examination.

I tried to tell myself that it was probably nothing. First of all, the spot was tender and I had read that cancerous lumps aren't painful. Like a lot of women, I also had a tendency toward breast tenderness from time to time and the symptoms would eventually disappear. Still, this was a bit different and I made an appointment with my genecologist. After his usual thorough examination, he said everything looked fine but ordered a mammogram and recommended that the report be sent to a breast specialist at Mount Sinai Medical Center he described as "conservative".

The breast specialist at Mount Sinai found the lump immediately, appraised it carefully and told me a biopsy would have to be done in the hospital under general anesthesia. "What if the diagnosis is positive?" I asked. He replied "If you care a great deal about the way you look, you can just have the lump removed and have radiation. If you care about living a long time, you'll have your breast removed."

My anger centered on the choice offered—my vanity or my good sense. As a writer, I am a habitual file keeper. My mother had had a radical mastectomy for a malignant lump and, statistically, this put me at greater than average risk. Thinking that some of the stories about new and less drastic treatment might be useful one day, I started collecting articles several years ago. That file was to prove invaluable. Several of the articles I'd clipped mentioned the promising results from "conservative treatment"—lumpectomy followed possibly by radiation. Others pointed up the fact that early detection can be the critical factor for a woman in keeping her life and her breast.

I sought a second opinion from Dr. David Kinne, head of the breast service at Memorial Sloan-Kettering Cancer Center. He described the alternative lumpectomy-and-radiation treatment. Based on the way the lump felt, his clinical impression was that it did not have the usual characteristics of a malignancy and he suggested following it for a few weeks before performing a biopsy. On Dr. Kinne's advice, I also sought consultation from Dr. Wendo Logan, a Rochester, NY physician involved in interesting diagnostic work with ultrasound and low-dose mammography. When the thermogram she performed indicated abnormal heat in the breast, Dr. Logan proposed another mammogram on a special micofocus unit that gave, in effect, a two-times enlargement of the breast tissue. There, clear as a dime, was the lump with all the characteristics of a malignancy. I got back on the plane immobilized with fear and took this newest mammogram to Dr. Kinne right from the airport.

I saw Dr. Kinne at the foot of my bed in the recovery room: "Well, it was malignant", he said; "I'll see you later". He came back to my room around six that evening and said I'd had a small "in situ" and infiltrating tumor which he'd removed with a small margin of surrounding tissue. "Not a lot of cancer", but he recommended a mastectomy. I said I wanted to investigate radiation first and Dr. Kinne arranged for me to talk with a Memorial radiologist, Dr. Florence Chu.

I threw Dr. Chu all my questions; she was very patient and answered them all. "The key", said Dr. Chu, "is knowing into that group the individual patient falls—are minimal and temporary and, as far as inducing additional cancer, she explained that while continuous low doses of radiation can stimulate cancer, a high dosage prevents cell transformation thus inhibiting malignant-cell growth. My husband and I decided to go with radiation therapy under Dr. Chu.

I asked Dr. Kinne to do the lymph-node operation. He was formal but distant in the operating room; "It's your choice, Mrs. Spear" were the last words I heard. The operation was bigger than I'd bargained for in terms of the pain but the good news was that the cancer had not spread.

You feel absolutely nothing during breast radiation, apart from awe. The treatment itself was short and the side effects turned out to be minimal as promised. Since the lumpectomy-and-radiation treatment, I have had a mammogram once a year and an examination every 3 months with no recurrence of the malignancy.

It is extremely difficult to know everything there is to know about breast cancer. New therapies are being evaluated and promise much. The sort of lumpectomy-and-radiation treatment I received is not available everywhere. Women in smaller communities, particularly, may have to seek out doctors willing to treat them conservatively and perhaps travel to different cities. But the options are there if one pursues them and does not panic.

Thank you for the opportunity to testify here today and share my experience with new research and new options in the treatment of breast cancer, an epidemic disease among American women.

Mr. PEPPER. Mrs. Nixon, we'll be pleased to hear from you.

STATEMENT OF JANET NIXON

Mrs. NIXON. Thank you, Mr. Chairman.

Ms. OAKAR. Mr. Chairman, may I suggest that they try to use the mike with the two mikes as well so that it can be heard by the press?

Mrs. NIXON. I am Janet Nixon. I am from Palatine, IL, and I wish to thank the Subcommittee on Health and Long-Term Care for this opportunity to appear and to present some concerns I have as a breast cancer patient:

In presenting these concerns, I do not wish to be viewed as an advocate for nor a militant against any issue, but simply as a woman with breast cancer, who has a great deal of emotion and compassion for other women who have been affected or will be affected by this devastating disease.

I discovered a lump in my breast a year and a half ago. To try to describe my feelings at that moment, late at night, 3 weeks before Christmas, is almost impossible. Only another woman who has experienced that moment can really know and understand. Terror and anger, perhaps best describe it. Was it cancer? If so, what would happen to me? Would I die? Would I live? If I lived, what would my life be like? Would I have to lose my breast to save my life? Would I feel less a woman? Will my two daughters have to face this? What will happen to my close friends? Will this happen to them? How will they deal with it happening to me?

Most of these questions still remain unanswered.

Because it was 3 weeks before Christmas, I chose to keep my discovery of the lump to myself. I tried to keep the holidays for everyone else as normal as possible, knowing that if it was cancer, the holidays somehow would never be normal again, because cancer does not just devastate the one who has it, but because of its uncertainty it affects everyone to whom you are near and dear.

Somehow, intuitively perhaps, I knew it was cancer. I also knew quite by accident that there was a treatment for breast cancer that was an alternative to mastectomy, namely lumpectomy plus radiation. Things then really got difficult.

I used the next 3½ weeks to not only prepare myself for a possible diagnosis of cancer, but to read everything available to me as a lay person on methods of treatment for breast cancer. I learned many things. But the controversy that exists on treatment methods in this country only added another burden. I learned that good medical men strongly disagree on treatment methods and the data available on these methods. It soon became apparent that at least the initial choice of treatment to pursue would have to be mine. I was convinced by the data available that if detected early and if I

was a candidate for the alternative treatment and it would be as effective as mastectomy for me, that this would be the treatment that I would pursue.

After the new year, I proceeded along the normal channels of seeing an internist and having mammography. Breast cancer became almost a fact from that mammography. I sought out a surgeon who could be as comfortable with the data on the alternative treatment as I. A needle biopsy was performed and my fears were confirmed. I had breast cancer.

I was next seen by a staff of radiation oncologists. Everyone agreed that, in fact, I was a candidate for lumpectomy and radiation, and at that moment my decision was made. If I could preserve my breast, the alternative treatment was no longer my alternative, but my treatment of choice.

I had the lumpectomy, the radiation, and the radium implant, and today I am well. But, nonetheless, I am and will always and forever be a breast cancer patient with all the fears that accompany that.

My experience is simply stated, but as I have tried to point out, it was not so easily achieved. Information is not clear, controversy is great, choices are agonizing and hard. And all this in addition to the burden of just finding out that you have cancer, the most dreaded of the diseases.

I don't know that I could have managed without the complete support of my husband and my family, who had their own unanswered questions, and the support of my friends who encouraged me in spite of some doubts, or the friends who saw to it that because my arm was temporarily affected and I couldn't drive, that I got to my daily radiation treatments. Most of all, I know I couldn't have managed without those who were there simply just to cry with me.

During all of this, some things became clear. The number of women affected by this problem is large. One in eleven American women will develop breast cancer sometime in their lives. It is the leading cause of cancer deaths in women. It is rare in young women and becomes more common as women grow older.

I could not help but think of the older women who make up the majority of breast cancer patients, who perhaps did not have the means nor the strength to pursue a decision as I did, a decision that was left for them. When cancer is diagnosed, we ask why. Was it genetic? Was it our environment? Was it the additives in our food, the hormones in our chicken, the PCB's in our fish? Was it a trauma that caused stress to weaken our immune system?

The causes of breast cancer have been attributed to many things. However, despite all of the research aimed at finding the cause, this avenue does not seem to hold any great promise for us in the immediate future.

Next to finding the cause, the most important aspect in combating the disease seems to be to find it in an early stage when the prognosis for cure with appropriate therapy is excellent. I firmly believe that earlier diagnosis would happen if the breast cancer treatment controversy in this country would be resolved and put to bed. Then women could be informed that if they religiously practiced breast self-examination, had their physician recommended

mammography and exams, and thus detected any breast cancer early, that then and only then most of them would be rewarded not with mutilating surgery, but with a treatment that would leave their breasts intact and the length of their life uncompromised.

I have recently been involved in starting a support group in our area for women with breast cancer who are considering or who have had the alternative to mastectomy. I know from that experience the concerns they have. Proven information and cost factors are great concerns. What happens to the older woman, who is most likely to develop breast cancer, living only on Social Security, who does not have the money to follow the American Cancer Society's guidelines for early detection leading to better prognosis? The guidelines include recommendations for early mammography and physician exams. Medicare does not cover this cost for her. Why?

It seems to me that if these guidelines for early detection have been developed, that a country like ours should be able to provide the wherewithal to the women in our lives to whom we owe so much. The greatest concern, however, of all remains that with all of the knowledge, technology, and treatment techniques available to us, our survival rates have not significantly improved in many, many years. No cure has been found.

We hope and pray for that daily. But if early detection is all we have today to improve our survival rate, then we must all be responsible and ensure that this information and the means are available to everyone.

I have attempted to tell you how difficult the situation can be to a younger women, who still has physical stamina, a husband who is alive and well, and family and friends who are able to help and support her. But picture the older woman, a woman with limited income, perhaps without a husband, and with friends that have problems that accompany their aging bodies, rendering them unable to help her. Does she deserve to be compromised? Isn't breast cancer enough? Must cost be a factor also? I don't think so, not in this country, not today, not ever.

Again, I thank you.

Ms. OAKAR. Terrific.

Mr. PEPPER. Thank you very much, Mrs. Nixon. That's excellent. Next is Mrs. Carolyn Alford.

STATEMENT OF CAROLYN ALFORD

Mrs. ALFORD. Thank you for this opportunity.

On Thanksgiving Day in 1974 I chatted with my mother while washing dishes, after the traditional family feast. Mother told me that she had read how you could detect breast cancer by examining yourself with a soapy hand while bathing. Later, after a shower, I told her that I had found a lump. She tried to assure me that the lump was simply due to the fact that I was pregnant.

The following Monday I had my regular prenatal checkup with my gynecologist, who said it was most likely due to a milk gland. But he would like for me to have it checked by a surgeon as soon as I delivered the baby.

My fourth child, Rick, was born January 15, 1975. Within an hour after his birth, a surgeon examined my breast and said it was

just a harmless little lump. But he would like to see me in 6 weeks. At this visit he assured me that it was nothing to worry about. He even commented that it was getting smaller. He asked that I come back in a month. The month passed and I returned. The surgeon, showing little concern, said it was unchanged and harmless. I then asked that he remove it, for my peace of mind. He called the hospital and arrangements were made for admission on the 13th of April, removal on the 14th, and I would go home on the 15th.

The morning of surgery I felt like I needed to know a few answers. So I asked if he thought everything would go OK in surgery. He replied, "Why, you'll be talking to your husband by 10 or 10:30." That is as close to a mastectomy as the conversation ever went.

I woke up to a horrendous, burning pain from my armpit to my waist, caused by over 200 stitches. The clock said 4 o'clock. No one had to tell me. I knew the worst had happened. I not only lost my breast, both pectoral muscles, the chest wall, the lymph glands under my arm. I lost control. Just because a person is put to sleep he should not lose control of the life. The surgeon paged my waiting husband, had him sign an additional consent form, and proceeded with this surgery. My tumor measured only 1½ centimeters and the malignancy had not spread.

There was no good medical reason for emergency surgery. Because I had four children, ages eight and under, I was sent home early. I returned to his office in a week to have my stitches removed. As he removed my last stitch he stepped back and exclaimed, "It's beautiful." I wept.

I had been home a week when a friend, who is a nurse, came to visit. And she asked if I had had a radical. I replied, "Helen Mae, I had a mastectomy." She then explained to me the various ways of removing a breast. When my husband came home I asked him if he knew there was more than one way to remove a breast. And he said no. We both felt so ignorant.

I felt then and I feel now that I have not been treated like a human being. I feel hurt and angry that this "noted" surgeon would put so much thought and pride into what he can do with his knife, with little or no empathy, understanding, or consideration of the person he has chosen to mutilate. I have since learned that there are approximately 15 types of breast cancer, and treatment alternatives may vary. I have just recently learned that frozen sections are not always accurate.

Every woman's situation is unique and she is the only one who will have to live with that decision for the rest of her life. There is no simple, single, solution. We must give the women of America the right to make that choice. We must ensure them the right to understand what their alternatives are and what these alternatives mean. The surgeon merely collects his fee and continues his business as usual.

There are those who would say, "Just be happy you're alive." That's not the point. The point is the quality of my life would have been greatly improved if I had been offered, and I would have accepted, an alternative to this surgeon's treatment.

I have three daughters. I am here today to ask your support to guarantee them protection from ever having to suffer this inhu-

mane and barbaric treatment. If just one unnecessary surgery is done a year, it's one too many. Unfortunately, I talked to at least one lady a month from my home in Richmond, who has suffered through a radical mastectomy. If the doctors are doing what they should be doing, they would not fear this bill.

This concludes my statement and I would like to now give you my husband's version and what effects my operation had on him. There's a common misunderstanding that the mastectomy is only a woman's problem. But it's a problem involving men too. The following is a letter prepared by my husband, and given to the Virginia lawmakers last December:

To all committee members, I regret that I did not speak at opening hearings. I chose to believe that my wife's shared experience and other similar experiences would be sufficient to press the committee into immediate action requiring two step informed consent prior to any form of breast surgery. This does not seem to be true so that I ask you to hear my experience.

In the late fall of 1974 my wife, a very healthy 31-year-old, was pregnant with our fourth child when a lump was discovered in her left breast. Removal of the lump was to be scheduled soon after our son's birth, which occurred in January of 1975. My wife was referred to a noted Richmond surgeon for this simple procedure. Numerous appointments for examinations were postponed because the doctor was in surgery. But all concern had been alleviated. We were assured of the commonness of the surgery, and at her age it would surely be benign.

I ask the committee to stop and think about this for a second. It took this doctor four months to find the time to see, examine, and admit my wife, and as you will hear later, he demanded the biggest decision of my life from me in just a few seconds.

On April the 18th my wife was admitted to one of Richmond's finest hospitals. I arrived early in the morning to see my wife before surgery. The surgeon came into the room to reassure her and together the three of us rode the elevator to the basement and the operating room. On the way down the surgeon suggested a couple of times that I go to work and she'll return in about three hours.

By that time he said I should find my wife resting comfortably. I insisted on staying and was told to wait in the lobby. I sat and waited as the morning hours passed. At approximately 12:30, over the noise of visiting hour traffic, I heard my name. I went to the receptionist desk and was told the surgeon wanted to speak to me. "Use this one," the receptionist said, handing me a phone slightly behind her. I was literally on my toes, leaning across the desk, visitors on either side of me, asking for room numbers, as the doctor said, "I'm sorry, Mr. Alford, but the tumor is malignant. I need your permission to perform surgery."

Completely shocked, off guard, standing in the middle of a circus, I simply said, "What choice do I have?" The terse return was, "I can return her to her room. We don't have much time." My reply was, "What do I do?" The answer: "Come to the bottom of the steps and someone will bring the form for you to sign."

I did, a man totally ignorant of the alternative surgeries, signed his wife over to a surgeon to perform radical mastectomy.

The ending is a horror story for modern medicine. Gone is a breast, lymph gland, pectoral muscles, chest wall, and over 200 stitches, for a lump 1½ centimeters. And the patient never had a choice of surgery or was even allowed to really believe she had a problem. My wife now lives a life of pain, restricted physical activity, and a never ending search for an acceptable wardrobe.

The impact on all the members of the family has been significant, and statistics say that this surgery often destroys homes and people in them. The Medical Society of Virginia would like us to believe that this can't happen, and even if it possibly could, it would be by some accident in some remote environment, not in the medical centers of Virginia. But it did happen, and happened here. This is not the last and only time.

This is in Richmond, an outstanding hospital. This was by one of Virginia's most respected and emulated surgeons. Who was I to question? I had provided the very best for my wife. What law or what procedure protects my wife from my ignorance and grants her control over her life? What procedure or law requires the surgeon to properly inform my wife of her alternatives? Explain to me, Medical Society of Virginia, how your literature laid out in a doctor's office, would have spared her this devastating treatment.

What the law allowed me to do and the surgeon to perform is unjust and inhumane. I sit in shock when I hear a Senator's commentary on his all-male committee saying, "We don't need this bill because we know what's best for women."

A spokesman for the Tidewater Medical Society testified that this is a feminist issue. The gall. How many Virginia men have been physically destroyed by the surgery?

The Virginia Chapter of the American Cancer Society joins with the Medical Society of Virginia to oppose this legislation, while knowing other states have already deemed it necessary and enacted protective legislation. I ask the members of the committee, how will you feel when the surgeon, after removal of your wife's stitches, stepped back and says to your wife, "It's beautiful"? This may be thought beautiful in medical terms, but in human terms this statement is incomprehensible.

My great regret is the large number of women who have had equally horrible experiences, but will not testify. They call, they talk, they spiritually support, but they hide lest anyone know what has happened to them.

I would like to touch on what seems to be a key point in the Medical Society of Virginia's suggestion that literature and education, co-produced with the Cancer Society, is a simple and easy solution, requiring no legislation. They suggest, and I remain amazed at the Medical Society of Virginia's attempt to paint a picture of all its members as kindly, loving, family doctors, quietly counseling all their patients. My own experience shows a highly efficient business person, three rotating examining rooms for speed and efficiency, desktop computers calculating the most profitable areas of the practice, and accountants with personal corporation tax laws to assist them financially.

These doctors and surgeons are a simple mix of people like the rest of us, subject to all the standard weaknesses of character, shortages of professional skill, lack of integrity. History has proven the need for laws to protect its citizens from the unethical, greedy, or incompetent, and the women of Virginia deserve protection from this barbaric treatment.

The law today offers greater protection against mutilization to the mentally ill than it does to women with breast cancer.

In conclusion, I would like to remind us all that no profession is above the law. Every profession is subject to regulation, including the medical profession. I would like to suggest that this legislation and this committee could learn the truth by requiring Virginia hospitals to share their five-year history record of breast cancer surgery. We would probably learn two things. First, the surgeons who perform breast cancer surgery can be categorized by the type of surgery they perform.

Second, the unfortunate women who were referred to surgeons performing radical mastectomies had very little opportunity to consider an alternative.

Thank you for your time and I would ask that you act immediately to enact two step consent legislation to protect women of Virginia.

Mrs. ALFORD. Thank you for listening. I have waited over 9 years to know that some one in Washington cares and is willing to address what is happening to American women with breast cancer. Thank you.

[See Appendix 1, p. 151 for additional material submitted by Mrs. Alford.]

Mr. PEPPER. Well, thank you very much, Mrs. Alford, for your very moving statement.

You will notice from the clock up there that we have received notice of a vote on the floor. We will have to recess so we can run over and vote. We will be back in just a few minutes.

[Brief recess.]

Ms. OAKAR. Senator Pepper is on his way but he has asked that we begin, because of the crunch on everyone's time. So our next witness is someone who, like the other witnesses are, is absolutely excellent and the author of many find books on the subject, Rose Kushner.

STATEMENT OF ROSE KUSHNER

Mrs. KUSHNER. Congressman Pepper in absentia, and distinguished members of the committee, ladies and gentlemen, I am curtailing my personal remarks because, again, breast cancer is being cut, one way or another. Our time has been shortened. I will only say that, like Mrs. Alford, I discovered breast cancer in 1974, but like Mrs. Spear, I was lucky enough to be a medical writer, and knew that there were alternatives to the radical mastectomy and that time a modified mastectomy and a two-stage procedure were just as hard to come by as a lumpectomy and radiation are today.

I am not going to speak any further personally, because of the time. I will speak because I have become a professional breast cancer patient. I was appointed in 1980 to be a member of the National Cancer Advisory Board, and therefore I think I can bring to the subcommittee and everybody here some points of view, both as a patient and as a member of the cancer establishment.

I'm delighted to be here because we women have been worried that AIDS is the only cancer that the Federal Government is concerned about. Now, AIDS is an entirely preventable cancer. So far it has attacked fewer than 5,000 Americans. But that's all we seem to be hearing about is AIDS. There is no reason that there should be AIDS. There is still no known way to prevent breast cancer. And as we have heard, the disease is epidemic in the United States with 115,000 new cases in 1984. One of eleven women living today will get it in their lifetime. And 38,000 American women will die of it per year.

While AIDS is a, quote, "new public health emergency," breast cancer has been killing women and men since the dawn of recorded medical history. Yet, since 1981 about $44 million has been spent by various government agencies to solve the AIDS puzzle, about $11,000 for each patient.

The National Cancer Institute's breast cancer budget during that same interval, from 1982 to 1984, devoted a little more than 400 research dollars for each of the 335,000 women who were diagnosed and treated for the disease during these 3 years. It comes to $137 million at its greatest.

While we certainly do not want to take anything away from AIDS research or from the victims of this mysterious and fatal disease, we do want breast cancer to get its fair share of funding. We need money to study the cause and prevention of breast cancer, and I have gone into great detail in my written testimony.

But I want to point out here that according to the Health Insurance Association of America, we Americans spend $355 billion on personal health care in 1983, almost 11 percent of our gross national product. The billion dollar budget of the National Cancer Institute is, therefore, only one-third of 1 percent of what we spent on personal health care in 1983. Now, how does breast cancer get its fair share of the research dollars?

The first thing we've got to know is what does breast cancer cost this economy? To assure that research dollars are allocated in proportion to cancer's real cost, the Congress should mandate an investigation to learn precisely how much money this devastating disease is draining from our Nation's economy. This is especially

important for breast cancer because most women always have breast problems that may be symptoms of the disease and we spend a lot of time and money running to doctors and having expensive tests to check what turns out to be harmless lumps and bumps.

But the statistical time clock for cancer cost does not begin to tick until the disease is actually diagnosed.

I would also like to ask that the Congress do something to restore the National Cancer Institute's requested construction budget so scientists can have modern and safe laboratories and equipment.

Since 1980 the allowed construction budget for the NCI has been only $1 million a year. These few construction dollars are supposed to pay for all buildings and fixed equipment required by all grant-supported activities in Bethesda, MD on the campus, as well as in the 59 cancer centers serving everyone in the country.

It is difficult for scientists to work in cramped laboratories, equipped with antiquated apparatus, and many are unsafe. Since 1980 the NCI's annual construction budget hasn't been large enough to improve its facilities to meet minimum EPA and DHHS safety standards. This subcommittee can do something about this situation because the National Cancer Act contains a provision giving the NCI a right to submit a bypass budget, directly to the President, so he can know how——

Ms. OAKAR. Would you explain a bypass budget, because I'm really concerned about the funding and our priorities. You mentioned a billion dollars for the Cancer Institute. That is four times less, more than four times less, than the cost overrun of one helicopter project just so the American people understand what we're talking about in terms of priorities. The cost overrun of one helicopter project it was supposed to cost taxpayers $4 billion and it cost them $8.6 billion instead; in 1 year, it went up that much, and that's 4.6 times less, or more, I should say, than what we give for cancer research. Are you ready for that?

I just think the American people ought to be outraged at our priorities in this Congress and by this administration.

Mrs. KUSHNER. I think the way to correct the priorities is to get the numbers about the cost of cancer, and the cost specifically for this hearing, the cost of breast cancer, because the dollars now are allocated according to various whims, let's put it that way, various directions individuals think are the way to go, and not on the cost of a disease to the economy.

Breast cancer costs a lot of money, in addition to these early detection costs. It's a chronic disease. Women have to be followed for the rest of their lives, and as we have all heard, so many of them are on medicare, and so the taxpayers must pay this expense.

I don't think that anybody knows how much breast cancer costs the economy. If we have 115,000 woman a year and we estimate that a minimum of $2,000, just for primary treatment, we're talking right there $230 million. I think my arithmetic is right.

Now, the bypass budget is a right that the National Cancer Institute, that the Director has, together with the National Cancer Advisory Board, to instead of sending the budget through channels, the NIH Director and then DHHS and then the Office of Management and Budget, we draft a budget to go directly to the President, and Congress has the right to see it, but you must request it.

Ms. OAKAR. I've got you.
Mrs. KUSHNER. Pardon?
Ms. OAKAR. I understand.
Mrs. KUSHNER. You've got the message?
Ms. OAKAR. Yes.
Mrs. KUSHNER. OK.
Ms. OAKAR. Thank you.

Mrs. KUSHNER. Another point was to establish inexpensive or, when necessary, free breast cancer diagnostic centers, to be sponsored by medicare. I think that has been adequately discussed here.

Another issue that has not been discussed is that we have no Federal regulation over the usage of medical radiation. Except for the developing fetus, the breast is the most radio sensitive of any human tissue. Mammography, therefore, should be done by equipment designed only for x raying breasts. But in 1980 more than two-thirds of all mammograms were done by general purpose machines, the kind used for looking for broken bones.

The Center for Devices and Radiological Health, formerly the Bureau of Radiological Health, is a division of the Food and Drug Administration for responsibility over radiation equipment. The Center does inspect x ray equipment twice, first in the factory and then after the components are installed in the hospital, clinic, or private doctor's office.

It also offers free advice and assistance by a program called BENT best exposure nationwide trend. But everything is voluntary, once the equipment is installed in a doctor's office. It is up to the States.

In 1978, I testified before a Senate hearing on the same subject, and I pointed out that at that time, as it is today, the baker whose scales give us 14 ounces of bread instead of a full pound is penalized, when the radiologist whose mammograph gives us overexposure to irradiation is not. It is outrageous that in the State of Maryland and in most States, the beautician who shampoos, cuts, and sets our hair must pass difficult qualifying examinations and be licensed, when x-ray technicians are not required to do so.

In 1978, only five States had licensure requirements. In 1984, 14 States have licensure requirements. Ohio is not one of them, nor is Florida.

In addition to these ideas for legislative action, I would like to ask this subcommittee to help us women by urging the FDA's Bureau of Oncologic Drugs to be more flexible about approving agents to fight breast cancer, when the surgery is not enough. While the FDA must ensure that medications are safe and effective, no substance now available for fighting any cancer meets these criteria. I mention this because approval of a substance active against breast cancer for certain women has been trapped in a bottleneck for several years, and I have planned to bring the matter up in detail at this hearing, and it is detailed in my written statement.

I have learned that approval of this substance for the treatment of early breast cancer may be imminent and congressional action may not be necessary. But new anticancer agents are always being developed and submitted to the FDA at various stages for approval,

and if it wishes to do so, this subcommittee could be valuable to clear up future bottlenecks.

In conclusion, I want to point out that a decade ago it was unthinkable that the NCI would spend millions of dollars to study a possible relationship between vitamins and minerals, and cancer. Today the chemo prevention branch is one of the Institute's newest and most exciting programs.

Ten years ago even hinting that a high fat diet might play a role in the cause and cure of breast cancer was medical heresy. Today the NCI is supporting two multimillion dollar clinical trials to prove or disprove this theory. And Dr. William B. Kohle, a scientist whose Kohle's toxins, not too long ago, were called quackery, is now being hailed as a pioneer of the era of immune therapy and biological response modifiers such as interferon.

If the NCI had enough money to support innovative, relatively low-priority research according to our times, we might learn that bacteria, microbiotic diets, stress, grief, and other, quote, "unproven methods" are, indeed, related to the cause and cure of breast cancer.

We must always remember that yesterday's quackery may be tomorrow's breakthrough.

Thank you.

[The prepared statement of Mrs. Kushner follows:]

TESTIMONY OF ROSE KUSHNER, EXECUTIVE DIRECTOR, BREAST CANCER ADVISORY CENTER, KENSINGTON, MD

Congressman Pepper, Distinguished Members of the Committee, Ladies and Gentlemen. My name is Rose Kushner, and I have been a medical writer longer than I want to admit publicly. In 1974, I was treated for breast cancer, and—after writing an article about my difficulties in finding state-of-the-art diagnosis and treatment ten years ago—I was asked to write a book about breast cancer. I began the Breast Cancer Advisory Center (BCAC) in 1975 to help women—and men—who needed information about all aspects of this disease.

From 1975 until 1982, the BCAC had a "hotline" as well as a mail service, and its telephone number and address received a great deal of publicity. As a result, during the past nine years, I have been contacted by about 20,000 women, and men, who either had, or were worried about having, breat cancer.

I was appointed to a six-year term as to the National Cancer Advisory Board (NCAB) by President Jimmy Carter in 1980, and since then, I have had the unique experience of being part of the so-called "cancer establishment," while—at the same time—I still hear from worried people who wonder why there is still no vaccine to prevent breast cancer or any way to cure this disease.

Before beginning, I would like to emphasize that I am testifying before this Subcommittee as an individual and not as a representative of the NCAB: my opinions are my own and do not reflect those of the Board or of the National Cancer Institute (NCI). However, I will be giving the subcommittee some information I would not know if I did not have the opportunity to be an "insider" several times each year. None of this information is confidential or secret: it is simply not generally known. For example, there is an annual "bypass budget" that the NCI submits directly to the President, but few people are aware of this direct-line between the Institute and the Oval Office.

Most of my testimony, however, will be based on my experiences as a breast-cancer patient. And, speaking for women who are living with this disease, I want to congratulate this Subcommittee for conducting this hearing. As far as I can recall, the last Congressional inquiry into breast cancer took place on May 4, 1976 under the sponsorship of the Senate Subcommittee on Health of the Committee on Labor and Public Welfare.

A great deal has happened since then, and much more could be done now because of the knowledge scientists have accumulated during the past twelve years: the identification of oncogenes, a technique for growing monoclonal antibodies to be at-

tracted to cancer cells, the way cancer spreads . . . . the NCI's 1985 research agenda is itemized in an attached booklet, "The National Cancer Program."

This hearing has also been encouraging, because many of us were beginning to believe that AIDS—an almost entirely preventable disease that has, so far, attacked fewer than 5,000 Americans—is the only cancer the Federal government is concerned about. There is still no known way to prevent breast cancer, and the disease is now epidemic in the United States: 115,000 new cases are expected in 1984; about one of every 11 women living today will develop breast cancer in her lifetime. In 1984, about 38,000 women will die of it.

While the AIDS mystery taunts scientific detectives as a "new" public health emergency, breast cancer has been killing women, and men, since the dawn of recorded medical history. Yet, since 1981, about $44 million has been spent by various government agencies to solve the AIDS puzzle—about $11,000 for each known patient. The NCI's total breast-cancer budget for 1982, 1983 and 1984 was about $138 million. But since an estimated 335,000 women will have been diagnosed and treated during these three years, this means about 400 breast-cancer research dollars were devoted to each new patient.

We certainly do not want to take anything away from AIDS research or from the victims of this mysterious, fatal disease, but we do want breast cancer to get its fair share of funding too. So more money for research is at the top of the list. As I said in my verbal testimony, I do not think the National Cancer Institute's 1985 budget of $1.1 billion are many dollars for our rich nation to invest to wipe out a disease that causes the deaths of 480,000 Americans every year. According to James L. Mooresfield, President of the Health Insurance Association of America, we spent $355 billion on personal health care in 1983—almost 11% of the U.S. gross national product.

Therefore, the billion-dollar budget of the entire National Cancer Institute accounted for only one-third of one percent of this huge sum of healthcare expenditures. The 1983 research budget for breast cancer was about $47 million, a miniscule fraction of one percent of the $355 billion spent for personal health care that year!

Earlier, I suggested that $400/patient seems to be too little money for breast-cancer research. But this may not be true. No one knows how much money should be spent on any cancer, because no one has ever measured the actual dollar costs of malignant diseases to the U.S. economy. In order to calculate how many dollars should be allocated to breast-cancer research, its direct and indirect costs—including money and time spent seeing doctors for examinations and expensive tests for symptoms that are not due to cancer—must be counted. And what about cuts in pay, babysitters, gasoline and parking fees? Should a patient's husband add his expenses and lost time to the country's annual breast-cancer bill?

After the disease is treated, "cured" women face a lifetime of followup examinations and tests to see if the cancer has recurred. Again—time lost from work, babysitters, gasoline and parking fees. These are as much a part of the cost of breast cancer as the doctor's bill. Yet they are not included in the latest report from the National Center for Health Statistics.

And, as Dr. William E. Powers states in his letter (attached), breast cancer is especially expensive to society. About twenty percent of all new patients are under the age of 50, when their contributions to their families and the economy are at their peak. But in the eighty percent of women who are older than 50, breast cancer is a relatively slow-growing, chronic disease. Women can suffer from breast cancer for decades, draining their personal and family resources—and those of Medicaid and Medicare—for examinations, treatments, rehabilitation, continuing care and hospice.

Until all costs of having breast cancer are computed, the NCI cannot know how to distribute its research dollars proportionate to the money this devastating disease drains from our nation's economy. This is why I have suggested that this subcommittee mandate a thorough investigation of both the annual direct and indirect costs of breast cancer, including the money spent for the diagnosis of a benign disease.

Such a study should be done to learn the real costs of all cancers.

There is another obstacle that has to be overcome before we can decide what to spend money for in breast-cancer research; the total construction budget of the National Cancer Institute has been $1 million per year since 1980. These few construction dollars are supposed to pay for buildings and fixed equipment required by all grant-supported activities on the 'campus" in Bethesda, Maryland, as well as in the 59 free-standing cancer centers caring for Americans throughout the United States.

This Subcommittee will be hearing about the need for intensified research to investigate exciting, new leads; you will hear requests that nontraditional approaches

to prevention and therapy be studied. But no research can be done in cramped, dingy laboratories with antiquated equipment.

Although a survey conducted in 1978 showed that $25 million was needed for each of the following five years to correct this problem, the NCI's annual construction budget, since 1980, has not been large enough to improve its facilities to meet minimum EPA and DHHS safety standards!

Now, thanks to contributions from Dr. Armand Hammer, Chairman of the President's Cancer Panel, and the American Cancer Society, the NCI has $150,000 for an independent survey of buildings and equipment needs. It is expected that this study will show that in 1985 dollars, $50 million annually will be required for the next five years. Will the government ignore recommendations from this survey as they did in 1978?

This does not have to happen. The Congress has the authority to prevent a repeat of 1978. In the National Cancer Act, there is a provision which gives the NCI the right to submit a "bypass budget" directly to the President. This was included in the law so the Administration would know how much money the NCI really needs to carry out its Congressional mandate. While all members of Congress have the right to see this document, you do not get it unless you specifically ask for a copy.

In the FY 1984 bypass budget, the NCI—with unanimous support from the National Cancer Advisory Board—requested $20 million for construction. Yet for the fifth consecutive year, this was again slashed to $1 million. I hope all members of this subcommittee will follow through and help solve this dilemma.

Let us assume that a cost analysis does show breast-cancer research to be greatly underfunded and that facilities are first-rate. What could the added money be used for to help us?

Without any hesitation, I would ask for research to develop a vaccine.

Scientists have known of a virus that causes breast cancer in mice, the MuMTV or murine mammary tumor virus, since 1936. But a subsequent search for a human virus led nowhere: no screen for high-risk women, no way to detect the disease early, no vaccination or antibiotics. The reason, I have been told, is that the millions of dollars spent convinced scientists that human breast cancer is not caused by a virus. Yet in 1974, a "particle" in the milk of a patient, a "particle" that appeared to be identical to the MuMTV when analyzed by sophisticated equipment, was discovered. What happened to this research? Ten years ago, scientists did not have today's technology to search for a human mammary tumor virus. I would urge the NCI to repeat the experiments done decades ago with the space-age apparatus available in 1984.

The NCI could also spend money on research I know many members of this Subcommittee find important: the possible role of bacteria in causing breast cancer; the effectiveness of macrobiotic and other anti-cancer diets; megavitamins; alternative therapies, like immunology; and various stress-reducing, relaxation techniques. After discussing these with several NCI program directors, I believe these would be studied if the budget were not already stretched taut so that higher-priority research can be done.

In addition to these, there are more traditional and conventional areas that need to be investigated. I have already mentioned a possible vaccine based on the murine mammary tumor virus; there are others.

CAUSE AND PREVENTION

(1) I have been told that nothing is known about the biology of the normal breast. Without this knowledge, it is impossible to know why some women are at high-risk when others are not: all "risk factors" known now are based on epidemiological studies of various populations. Unless scientists know more about healthy breasts, they cannot understand why their cells go berserk and become malignant—or, for that matter, develop into a benign disease.

(2) It has been estimated that about five percent of all breast cancers are hereditary, and there are scientists trying to identify a specific breast oncogene. Once this is done, restriction enzymes, gene-splicing and other technological miracles of in molecular engineering may make it possible to remove or "defuse" this oncogene and prevent almost 6,000 breast cancers annually.

(3) An accepted low-risk factor is giving birth to a first child before the age of 20; an accepted high-risk factor is giving birth to a first child after the age of 30. Unless there is a scientific breakthrough, we in the United States can expect breast cancer to erupt as a national emergency in ten or fifteen years.

Why?

Since 1975, the number of women waiting to begin their families until they are 30-35 years old has doubled, and the trend is continuing to grow. Scientists must find a safe way to simulate the protective effects of early pregnancy on the breasts to avoid an epidemic among tens of thousands of older, first-time mothers.

(4) Recent surveys from NCI's cancer registries have shown that black women have poorer prognoses than their white sisters have. While this was once attributed to later diagnosis, more advanced disease and poorer care, it is now known that this is not so. Even when black and white women are matched by age, stage of disease at diagnosis and treatment, black women are more likely to die of breast cancer at an earlier age. Research in this area is imperative.

(5) The hypothalamus of the brain is the seat of emotion. It is also the part of the brain that triggers the secretion of the many hormones that are suspected of being involved in the cause of breast cancer. Not long ago, it was impossible to measure the quantity of these hormones in blood or urine, but now technology is available to actually weigh or count substances known to be associated with stress, anger, grief, etc. Dollars spent for research in this area might help prevent the disease from developing—or even cure it.

(6) There are data showing that "chronobiology" may play an important role in improving the effectiveness of anti-cancer therapies. Most therapies act against a cancer cell when it is "twinning," when its DNA separates to form two daughter cells. Unfortunately, healthy cells that are twinning at the same time also suffer, and this is why radiation and chemotherapy may have toxic side-effects. Chronobiological research is based on the hypothesis that our physical processes—except for cancer cells' growth—slow down when we are asleep, suggesting that therapies should be less harmful to healthy cells if they were given nocturnally.

(7) Finally, I must repeat that we desperately need a vaccine to protect us. Like the cowpox inoculation that prevented human smallpox, the MuMTV may become a safe vaccination.

EARLY DETECTION

(1) While NASA scientists can see what is happening on the moon, doctors have no way of knowing if a lump in a woman's breast is benign or malignant. Yet finding a tumor early is the only way we women can, at least, prevent death from the disease. Doctors are also unable to know if a woman's underarm (axillary) lymph nodes contain cancer cells without cutting them out and looking at the tissue under a microscope.

Early detection of a metastasis—spread of breast-cancer cells to another organ—is rarely discussed, but it is vital to diagnose and treat such a secondary tumor early. But in almost all cases where the disease has spread, the metastasis is not found until the secondary tumor is large enough to cause symptoms. Diagnosing a breast cancer when it is only a cluster of a few cells, identifying malignant lymph nodes without surgery and finding metastases when they are small enough to be destroyed should be possible today.

One method may involve the use of monoclonal antibodies; another may be identifying molecules of cancer-associated substances—"markers"—in blood and urine that may be signs that there is cancer growing somewhere in the body. Research is needed.

(2) Until this research has proven to be successful, X-raying the breast—mammography—is the most reliable early-detection tool available. In 1977, a panel of experts, convened by the National Institutes of Health, recommended annual X-ray breast-screening examinations by mammography for all women older than age 50. In spite of this NIH recommendation, Medicare will not pay for such annual diagnostic examinations: the expense of X-raying the millions of women over 65 is the reason. Dr. Philip Strax, a radiologist who is present at this hearing, has found a way to take four views of a woman's breasts for $25. By using his cost-effective methods, a Medicare-sponsored, early detection program should be possible.

(3) Except for a developing fetus, the breast is the most radiosensitive of any human tissue. Mammography, therefore, should be done by equipment designed only for X-raying breasts. Yet in 1980, more than two-thirds of all mammograms were done by "general purpose" machines, the kind used to look for broken bones.

The Center for Devices and Radiological Health—formerly, the Bureau of Radiological Health—is the federal agency responsible for radiation equipment. It does inspect X-ray equipment twice: first, in the factory and then after the components are installed in a hospital, clinic or private doctor's office. It also offers free advice and assistance via a program acronymed BENT (Breast Exposure, Nationwide Trends).

but involvement with BENT is voluntary. The federal government has no regulatory authority over the usage of ionizing radiation equipment.

Instead, state governments are supposed to monitor the quality and condition of the equipment, the film, chemicals, certification of technicians, etc. Most states' radiation-control offices are understaffed and underfunded; checking mammography equipment is often at the bottom of their lists of things to do. At a 1978 Senate hearing, I also asked for federal regulation of diagnostic radiology, and what I said then still applies today:

"It is outrageous that the baker whose scales gives us 14 ounces of bread instead of a full pound is penalized when the radiologist whose mammograph gives us overexposure to irradiation is not. It is outrageous that the beautician who shampoos, cuts and sets our hair must pass difficult qualifying examinations and be licensed when X-ray technicians are not required to do so."

Except for the fact that 14 states and Puerto Rico now require X-ray technicians to be licensed, we, the people, are no better off in 1984 than we were six years ago. Our "watchdog" over radiation needs some teeth, so our breasts have as much protection as our bread has.

DIAGNOSIS

In spite of all the hopeful early-detection methods I mentioned earlier, the present state-of-the-art is that a biopsy—removal of tissue for a microscopic study—is the only way to make a reliable diagnosis of breast cancer. In June, 1979, an NIH international Panel of breast-cancer experts recommended that the diagnostic biopsy be separated from further treatment to give women enough time to get second opinions about the diagnosis, alternatives to mastectomy and—most of all—to adjust to the knowledge that they have breast cancer.

While this "two-stage" procedure has been adopted in many parts of our country, thousands of women in the United States are still required to sign a form giving the surgeon permission, before the biopsy, to do a mastectomy if a quick study of a frozen sliver of the tumor shows cancer cells. They then wake up to discover that their breasts were amputated while they were unconscious. In addition to the unnecessary psychological pain this causes, a biopsy using full operating-room regalia is much more expensive than one performed as an out-patient with either local or general anesthesia. By discouraging this barbaric practice, Medicare would also reduce its spiraling costs.

TREATMENT

(1) At the same conference in which the two-stage procedure was advocated, the NIH panel also recommended that the Halsted radical mastectomy—the operation in which a woman's chest (or pectoral) muscles are removed—no longer be the standard primary treatment for all cases of breast cancer in the United States. In spite of this, a 1982 American College of Surgeon's survey of 757 hospitals showed that 3.4 percent of 1981's estimated 110,000 cases—more than 3,500 women—were victimized by Halsted radical mastectomies. Since then, some states have enacted legislation to prevent the railroading of women into extensive surgical procedures. Medicare could help those older than 65 to avoid the Halsted radical by not reimbursing surgeons who remove the muscles unnecessarily.

(2) Another important issue in the treatment of breast cancer involves swift approval by the Food & Drug Administraton (FDA) of effective substances to fight the disease, when surgery is not enough. While the FDA must ensure that drugs are both safe and effective, there should be some flexibility where anti-cancer agents are involved. FDA approval of a non-toxic anti-estrogen (tamoxifen) for certain women found to have malignant axillary lumph nodes has been trapped in a bottleneck for several years, and I hope this subcommittee will look into this important matter. When FDA approval is "signed off," the label on tamoxifen will indicate that it is useful for the treatment of early breast cancer as well as for advanced disease.

I would like to conclude by pointing out that a decade ago, it was unthinkable that the NCI spend millions of dollars to see if vitamins and minerals could prevent cancer. The Chemoprevention Branch, however, is now one of the Institute's newest and most exciting programs. Ten years ago, even hinting that a low-fat diet might prevent breast cancer was heresy; today, the NIC is supporting two multimillion-dollar trials to prove—or disprove—this theory.

And Dr. William B. Coley—a distinguished scientist whose "Coley's toxins" were, not too long ago, considered quackery—is now hailed as a pioneer of a new era of immune therapy using Biological Response Modifiers such as interferon.

If the NCI had enough money to support innovative, relatively low-priority research, we might learn that macrobiotic diets, stress, grief and personality do have something to do with the cause or cure of breast cancer. We must always remember that yesterday's quackery could well be tomorrow's breakthrough.

SUMMARY OF SUBCOMMITTEE ACTIONS SUGGESTED

(1) Mandate a thorough investigation of both the annual direct and indirect costs of breast cancer, including all money spent to rule out the presence of disease.

(2) Request the NCI's annual bypass budgets and see to it that enough money is appropriated to assure scientists modern and safe laboratories and equipment.

(3) Establish inexpensive—or, when necessary, free—breast-screening centers sponsored by Medicare.

(4) Draft legislation giving the federal government the right and responsibility to regulate all aspects of usage of medical radiation.

(5) Require Medicare to offer incentives (and disincentives) to encourage surgeons to do a two-stage, biopsy first/treatment later procedure; require that Medicare develop and distribute educational materials for newly diagnosed breast-cancer patients so they may learn about state-of-the-art alternatives to mastectomy, along with their advantages and disadvantages.

BREAST CANCER STATISTICS IN THE UNITED STATES

Breast cancer is all women's most dread disease.

About 115,000 new cases of breast cancer are expected in 1984.

One of every 11 U.S. women will develop the disease.

About 1,500,000 women annually see a health professional about a breast problem.

Nine of every ten breast-cancer "symptoms" are benign.

More than 400,000 women annually need surgical biopsies to be sure of the diagnosis.

About 1,000,000 women alive in the United States, in 1984, have been or are being treated for breast cancer.

Breast cancer incidence peaks between the ages of 44 and 55, but it has been increasing in women under 35 since 1974. A woman's risk rises with age.

Giving birth to a first child after the age of 30 elevates risk.

As explained in Alternatives, breast cancer is a "disease of affluence," primarily attacking urban, upper-income women.

The highest-risk areas are: the East and West Coasts, especially the Northeast; the regions bordering the Great Lakes and retirement communities in Sunbelt states.

In most countries, Jewish women of European ancestry (Ashkenazic) have higher incidences than other populations.

Ms. OAKAR. Thank you. The Senator has asked me if I would just lead into one or two quick questions for all of you.

I was struck by your last statement. In other words, there are some new ideas, diet being one of them, not that it's a cure, but that it certainly could be a major help.

I just want to ask one question and anyone can answer it, because of our time restraints I want to perhaps ask you more questions for the record, in writing.

What would you like to see happen? What do you consider the major breakthrough? Does anybody have any ideas on this? What would be the major breakthrough for you?

Mrs. KUSHNER. A vaccine.

Ms. OAKAR. Do you think it's possible?

Mrs. KUSHNER. Sure. We have had a mammary tumor virus discovered since 1936, discovered by Dr. Bittner in Minnesota. It was very exciting at one time and the research was dropped because I understand scientists say no virus causes cancer. But they didn't have the equipment and knowledge we have now about oncogenes.

It's ridiculous not to go redo those experiments. The scientists are not being funded to look for a vaccine.

Ms. OAKAR. So you think it's within our reach?

Mrs. KUSHNER. I certainly do.

Ms. OAKAR. Rose, this isn't just to promote you, but you probably know as much about this disease as anybody I know of, and all of you collectively are just fantastic.

What's the name of your books?

Mrs. KUSHNER. The first one was called "Breast Cancer: A Personal History and Investigative Report." The second two were called "Why Me?" and the last one is "Alternatives and New Developments in the War on Breast Cancer."

Ms. OAKAR. Anyone can take this. What one piece of advice would you give anyone at all, to an American woman who was fearful of this disease? Janet, did you want to answer that?

Mrs. NIXON. Rose has a booklet which we published for NCI. And we use it in our support group. It's called, "Have You Ever Thought About Breast Cancer?" and I do believe that every woman should. Whether they're afraid of breast cancer or not. This affects a lot of women. They need to read it and as she suggests, put it in a drawer and hope you never have to use it. But if it's there, it's there.

I think women should try to be informed. We are no longer living in an age where information is not available. But first you have to know that there's information out there to seek.

Women—no one—by the way, if you wish to obtain a copy of this booklet, it's free.

Ms. OAKAR. Where do you get it?

Mrs. NIXON. From the 1-800-4 CANCER number from NCI.

Ms. OAKAR. So, there's a hotline?

Mrs. NIXON. There's an 800 number, 1-800-4 CANCER.

Ms. OAKAR. OK.

Mrs. NIXON. I also want to say to Rose, she has helped countless women. Countless women. She does not know how she has touched our lives, all of us, at some point.

But anyway, the information is in her book. The information is in her literature. There are other books. Penny Weisbad. She has some excellent information.

But women who do not wish to speak the word "cancer" from their mouth, we cannot do that anymore. We have to know that we are victims of breast cancer, 1 in 11. We must be informed. And the time to be informed is not when you're devastated with a diagnosis. You need some basic information before.

Ms. OAKAR. So women should ask a lot of questions of their doctors.

Mrs. NIXON. That's right.

Ms. OAKAR. And if they're not satisfied, as Mrs. Spear did, you shopped around and you really studied it. You shouldn't, I guess, have to do that, but in this age when there are so many opinions, you're going to have to do that. It's not something to be afraid of, it's something that people should reach out for. Am I pretty right in summarizing that?

Mrs. NIXON. Yes.

Ms. OAKAR. Carolyn, I was very struck by your testimony. I think we were all really moved to empathize with your situation and we hope it never happens to another woman, and that's what we're trying to do with our legislation, on the Federal level. As you know, I'm introducing that legislation today.

What advice would you personally, having gone through that kind of devastation, what advice would you give to women?

Mrs. ALFORD. Well, I think a second opinion is very important, getting a second opinion. I think the doctors need to be informed more.

Ms. OAKAR. The doctors need to be more informed?

Mrs. ALFORD. The doctors. Sometimes I think we know more about what's going on than they do.

Ms. OAKAR. Well, I think that's—on that note, we're going to hear from some doctors now.

I want to thank all of you. I think it was just terrific. And the Senator would like to ask some questions.

Mr. PEPPER. Mrs. Kushner, I am sorry I missed most of your statement, but I read most of your written statement here.

You advocate a thorough study, a thorough investigation, of the total cost of dealing with cancer.

Mrs. KUSHNER. Yes, I do, indeed. I think that all cancers should be investigated, especially—now, the Center for Health Statistics, the National Center for Health Statistics, Dr. Tom Hodgson, says it costs $10 billion a year. Well, that's preposterous, because it does not include all the checkups to see if you have it or not. Now, how many women run to the doctor every month, every 3 months, "Let's talk only about breast cancer." Men can talk about their prostates but women talk about their breasts.

How many women run to the doctors every time they have a lump, pay $50, have a mammogram, not cheaply the way Dr. Strax does it, but for $200, and that doesn't go into the cancer cause? What about their babysitters? What about time lost from work? What about traveltime, gasoline, parking fees? That does not count unless it's cancer. And the same is multiplied for every other cancer there is.

As long as we go on the premise that cancer is costing this economy only $10 billion a year, and you're never going to get any more money for the cancer budget.

Mr. PEPPER. Do you think we should earmark some of the money for cancer that goes to the National Cancer Institute, for breast cancer detection and treatment?

Mrs. ALFORD. Yes.

Mrs. KUSHNER. Well, I think in general the line iteming or earmarking on a congressional level, should not be necessary and I would like to think that simply a strong expression of interest and urgency would be enough to get the NCI to do it, without actually putting it into legislation.

However, I am on the record with other issues, that if that is the only way to get money, then so be it. It should be earmarked.

I do not like line iteming. I think—I'd like to think that the NCI is run by responsible people who will listen to me.

Mr. PEPPER. Is any part of the cancer program that we're talking about here this morning included within medicare?

Mrs. KUSHNER. Pardon?

Mr. PEPPER. In medicare, is what we are talking about, the right of a woman to go to a doctor and get preliminary tests and——

Mrs. KUSHNER. No, no, unless it is cancer. If it is cancer, then it will be covered.

Mr. PEPPER. It's not covered by medicare?

Mrs. KUSHNER. No, if it's not cancer. If she goes in with a lump and it's benign, then it's not covered.

Mrs. NIXON. That's right.

Mr. PEPPER. That's what our bill, Ms. Oakar's and my bill, attempts to achieve.

Mrs. NIXON. Right.

Mrs. KUSHNER. Yes, indeed. I congratulate you on it.

Mr. PEPPER. The other incidental costs also should be covered some way or another, but the first thing is to structure things so that women can feel free to go to a competent person and get a checkup, repeatedly, to try to detect the beginning of a cancer before it gets too serious.

Mrs. KUSHNER. Well, certainly, women under medicare are all over 65.

Mr. PEPPER. What about the operation? That's not covered by medicare either, is it?

Mrs. KUSHNER. I beg your pardon?

Mr. PEPPER. The operation.

Mrs. NIXON. Mastectomy.

Mrs. KUSHNER. If a symptom is found, I do believe that medicare will cover it, even if it's benign. They will call it a benign disease.

Ms. OAKAR. Eighty percent, Mr. Chairman.

Mr. PEPPER. Well, that comes under part B.

Mrs. KUSHNER. The Federal Government——

Mr. PEPPER. Hospitalization.

Mrs. KUSHNER. The two pieces of legislation you have raised, I think, are the best ways to protect women in general and in, specifically, women over the age of 65, who, according to a 1977 recommendation from the NIH, should be mammographed every year. Well, I think the mammography should be regulated. But for women 65 not to have their screening paid for in this country is preposterous.

Mrs. NIXON. Right.

Mr. PEPPER. Maybe we should just try to provide that the detection and treatment of cancer, including breast cancer, shall be included within the services provided by medicare?

Mrs. KUSHNER. I certainly agree with you and I think that, as I've said earlier, men's prostates deserve as much protection or as little protection as women's breasts, whichever way you want to look at it.

Mr. PEPPER. It's a little bit off the immediate line that we are following here today, but we are very much concerned about the establishment of a medical care system in this country under which every man, woman, and child, by at least paying what they are able to pay, may be able to get the medical care that they should have. It doesn't look like it's politically possible to get national health insurance. Our subcommittee is pushing a bill to have them be allowed to use HMO's and we also have a bill to authorize

hospitals to become HMO's so as to enter into a contract with medicare for the performance of medical services. I'm gratified to learn that many insurance companies now are becoming HMO's. Do you think this would be an appropriate way to be consistent with American principles and ideals and everything, if we can establish some sort of a national medical program for all the people?

Mrs. KUSHNER. I think that we have to start with what we've got, which is medicare. Medicare is a national HMO for people over 65 and I think that the third party carriers in the private sector will emulate it, for example, with the diagnostic related groups for cost containment. I think that whatever you do for medicare will affect the whole population.

Mr. PEPPER. You all have testified that a good many of the women who are victims of this cancer are below 65.

Mrs. KUSHNER. Yes.

Mr. PEPPER. They are even in their fifties and all.

Mrs. KUSHNER. I think Dr. Philip Strax will address that question, if he ever gets a chance to get to this table.

Ms. OAKAR. OK.

Mr. PEPPER. Thank you all very much. May I join you, Ms. Oakar, in the warmest commendation of all of you ladies for your excellent statement this morning?

Mr. Andrews.

Mr. ANDREWS. No questions, thank you.

Ms. OAKAR. Thank you all very, very much and one thing you have communicated loud and clear is that there has to be better communication between the doctor and the patient. And then the breakthroughs and all the other fine things.

Thanks a million. You're just outstanding.

Our next witnesses are a panel of doctors, Dr. Ernst Wynder, who is president of the American Health Foundation of New York City; Dr. Barbara Threatt, who is with the Institute of Social Research and Michigan Cancer Foundation, of the University of Michigan; Dr. Charles Hubay, who is the professor of surgery, Case Western Reserve School of Medicine, I'm proud to say of Cleveland, OH; and Dr. George Crile, Jr., emeritus clinician of the renowned Cleveland Clinic, also of Cleveland, and we're delighted to have you gentlemen and ladies here. We'd be happy to hear from you, Dr. Wynder, first, I believe it is. You are first on the ticket.

PANEL TWO: CONSISTING OF ERNST L. WYNDER, M.D., PRESIDENT, AMERICAN HEALTH FOUNDATION, NEW YORK; NY; GEORGE CRILE, JR., M.D., EMERITUS CLINICIAN, CLEVELAND CLINIC, CLEVELAND, OH; BARBARA THREATT, M.D., INSTITUTE OF SOCIAL RESEARCH AND MICHIGAN CANCER FOUNDATION, UNIVERSITY OF MICHIGAN, ANN ARBOR, MI; CHARLES HUBAY, M.D., PROFESSOR OF SURGERY, CASE WESTERN RESERVE SCHOOL OF MEDICINE, CLEVELAND, OH

STATEMENT OF ERNST L. WYNDER, M.D.

Dr. WYNDER. Thank you very much. Mr. Pepper, Ms. Oakar, Mr. Andrews, it's a great privilege to appear before this committee. As you may know, I've been involved in the study of cancer epidemiology for some three decades, first at Sloan Kettering Memorial and

the last 14 years at the American Health Foundation, and if there's one thing I've learned, it's that cancer is not an inevitable consequence of aging. In other words, most cancers have identifiable causes.

I'm in agreement with a recent report from the National Academy of Sciences that the major cause for breast cancer is dietary fat. The reasons for this I have summarized in my formal report, where I have also listed a number of mechanisms which could explain the role of dietary fat.

We are recommending, not only for the reduction of breast cancer but also for cancer of the colon and prostate and probably ovary and endometrium, and certainly for the reduction of the major cause of death in our society; coronary artery disease, a reduction of our total fat intake to 25 percent of total calories.

I am pleased that the National Cancer Institute and the American Cancer Society have given much support to programs in nutritional carcinogenesis. In fact, this year the National Cancer Institute will launch two clinical trials to test the low fat hypothesis. One is directed to women at high risk for breast cancer, primarily based upon family history and fibrocystic disease of the breast, 6,000 women will be involved in a trial with a 20 percent fat diet.

In addition, post menopausal women with stage two breast cancer will be treated with a 20-percent fat diet to determine whether this degree of reduction in fat will improve survival of breast cancer as well as our epidemiological data indicated it will.

I would now like to suggest to you three specific recommendations. It was in 1950 that we first provided evidence that smoking was a major cause of cancer of the lungs. It was not until 1964 that this country, through a Surgeon General's report on smoking and health, brought this issue squarely before the American people.

I suggest to this committee that you ask the Surgeon General of the United States to work on a Surgeon General's report on nutrition and health. If this were done, the public, the food industry, and the scientific community, would be more inclined to follow the kind of recommendations that we and others have made.

I consider overnutrition in our society a major cause of excess death. It's unfortunate, as Rene Dubois pointed out some years ago, that in our society we suffer from malnutrition of the poor and malnutrition of the affluent at the same time.

The second recommendation I'd like to make, similar to one I made recently to the National Cancer Advisory Board, is to establish cancer control units in every clinical cancer center and every major hospital throughout the country. These units would consist of a health promoter, a nutritionist, a school health educator, a smoke cessation therapist, a behavioral scientist, and an economist. The targets of these cancer control units would be the school, the worksite, the hospital, and the community.

Only by providing this type of critical mass to cancer prevention and early cancer detection will we get the appropriate impact of preventive programs.

I suggest that these cancer control units be run primarily by allied health professionals. I believe that we, as doctors, are either under or over-trained to properly conduct preventive strategies. But these allied health professionals, like the barefoot physician in

China, can, in my view, make a major impact on preventive strategies that we must pursue.

Furthermore, I suggest that these cancer control units should be paid by the same sources by which currently pay for therapeutic services. A country that can afford to pay for all the coronary bypasses, all the pneumonectomies, can certainly and must pay for preventive services. This country will never have adequate preventive services unless we, as a society, provide the appropriate funding for preventive services.

The third recommendation relates to a fundamental finding that all of our health habits have their beginning early in life, whether it's smoking, nutrition, or physical activity. I like to recommend that we, as a society, make school health education a mandatory part of our school curriculum.

The American Health Foundation, has developed, with funding from the National Cancer Institute and the National Heart, Lung, and Blood Institute, a Know Your Body Program that starts in the first grade, and eventualty will run for 12 years. In the very first year, we give the child a health screening test, measure cholesterol, and blood pressure, and provide the child with a health passport.

We have found that by the time our children are 12 years of age, one-third already have one risk factor for chronic disease.

Clearly, a country that can send a man to the Moon, a country that can afford to make us militarily strong, must be able to provide our children with a chance to live into old age without being unnecessarily sick.

I always felt that the greatest gift we can give to our children is the gift of health. A sound, cost effective, school-based health education program in every school can make a major impact on the long-term health of our Nation, particularly, because our data, show that children have a major impact on their parents perhaps greater than we, as parents, have on children.

I regard, therefore, including what children learn about nutrition, what we teach them early in life, to have a lasting impact on the long-term health of our Nation.

Primary prevention is medically sound and, obviously, it is economically sound. Whenever we speak about spiralling health care costs, we need to recognize that the only way in which we can really reduce health care costs is by primary prevention. The health economist Victor Fuchs in an elegant booklet on "Who Shall Live" showed us many years ago that the State of Utah has far lower health care costs than the State of Nevada, primarily because of different lifestyle.

We have, Mr. Chairman, in the American Health Foundation a motto that I think you will find particularly appealing, which I borrowed from the old Greeks just to show that there are really few new thoughts under the Sun.

This motto says it should be the function of medicine to help people die young, as late in life as possible. I suggest to you that this motto can only be realized through the practice of primary prevention and will apply to cancer of the breast as well as to many other types of disease.

I thank you.

[The prepared statement of Dr. Wynder follows:]

PREPARED STATEMENT OF ERNST L. WYNDER, M.D.[1]

I appreciate the opportunity to appear before the Committee on Aging to testify on opportunities with respect to the prevention of breast cancer. Lifelong experience in epidemiology and preventive medicine has convinced us that for cancer, as for disease in general, prevention is obtainable and presents the ultimate goal of the scientific and medical research community. Clearly, at a time of crises in health care cost, prevention also provides the key economic health care goal.

Nutritional excesses, in terms of fat consumption especially in a largely sedentary population, represents a major risk factor for disease, including breast cancer. Nutritional research, nutritional education for all segments of society, and the establishment of nutritional guidelines must be supported and advanced if we are to reduce and eliminate diseases caused by faulty nutritional habits. Congress and this committee can help set the stage—the National Institutes of Health, the scientific community, and the food industry stand ready not only to conduct more research, but, based on the best available evidence, to implement a nutritional policy for all society.

Epidemiological evidence indicates that breast cancer is not an inevitable consequence of living and aging. The evidence from epidemiology also demonstrates, in a way consistent with laboratory experiments, that dietary fat is causatively related to the pathogenesis of breast cancer, and also affects the survival rate among postmenopausal breast cancer patients. The facts that have led to this conclusion may be summarized as follows:

1. There exists a significant correlation between the intake of dietary fat and the incidence of breast cancer in various countries.
2. As migrants from a low-risk country (such as Japan) move to a high-risk country (such as the United States), they experience an increase in breast cancer rates concomitant with their increase in dietary fat intake.
3. An increase in breast cancer incidence is noted in Japan consistent with an increase in dietary fat intake.
4. Several case-control studies have demonstrated a greater intake of dietary fat in breast cancer patients than among controls.
5. The causative relationship between nutrition and breast cancer applies to dietary fat intake rather than to caloric excesses.
6. The better survival rate of Japanese compared to American postmenopausal breast cancer patients is considered to be related to their lower intake of dietary fat.
7. In the laboratory animal setting, both saturated and unsaturated fat have been shown to enhance risk of breast cancer in rats initiated with a carcinogen.
8. Dietary fat can influence breast cancer susceptibility in a number of different pathways: by affecting the immune system; by modulating the makeup of cell membranes; by influencing cellular enzyme systems; by increasing the production of hormones such as prolactin and estrogen, and prostaglandins; by affecting receptors in target organs; by influencing the conversion of androstenedione into estrogen.

Mechanistic explanations for the effects of dietary fat on breast cancer are therefore at hand.

Because of this evidence and the evidence relating dietary fat to other cancers such as colon and prostate, and because of the role of dietary fat in the etiology of other diseases, we have recommended a fat reduction to 25% of total calories for the American people, beginning in infancy. American consumers need to be educated as to how they can best lower their dietary fat intake, and the food industry must be encouraged to reduce the fat content of their products.

A reduction of dietary fat to 20% of total calories or lower is likely to affect the survival rate of postmenopausal Stage II breast cancer patients. The National Cancer Institute is currently initiating a long-term trial on 2,000 such breast cancer patients. This secondary prevention trial and an additional primary prevention trial involving 6,000 women at high risk for breast cancer soon to be launched at the National Cancer Institute is designed to demonstrate that dietary change, even relatively late in life, can both reduce one's risk for breast cancer, and improve a postmenopausal breast cancer patient's survival. It is reasonable to assume, however, that dietary fat reduction will have its major impact on breast cancer if started very early in life.

It is for this and other health reasons that we at the American Health Foundation have developed the Know Your Body school health promotion program starting in the first grade. The basic purpose of this project is to teach children about their

[1] The author is President of the American Health Foundation, 320 East 43rd Street, New York, NY 10017.

body, promote in them a sense of self-responsibility and the ability to make healthful decisions. This program will hopefully lead to better health habits including those which in turn will improve our children's well-being and reduce their risk for a variety of adult-onset diseases including breast cancer.

It is our hope that as this committee centers its attention on short- and long-term preventive health strategies, it will focus on school health education through which we can also educate the parents and thus society at large. Effective school-based health promotion must become our major health priority if we are going to give to our children a priceless gift—the gift of lifelong health.

The National Cancer Institute is to be complimented for its attention to nutritional research in carcinogenesis. Congress should give high priority to nutrition as a key factor for providing a youthful longevity to our people. At a time of budgetary restraint it is particularly important to focus on efforts to prevent illness.

The history of medicine is replete with examples showing that the major triumphs over disease have come through the application of appropriate preventive measures. History will repeat itself in ultimately reducing if not eliminating the majority of human cancers on the basis of a preventive strategy.

Ms. OAKAR. Thank you very much, Doctor, for that excellent testimony.

Our next witness is Dr. George Crile, and Dr. Crile, you must have been as touched as all of us were, hearing Mrs. Alford's testimony about that radical surgery she had. Would you take the mike there, Doctor?

Dr. CRILE. Yes.

STATEMENT OF GEORGE CRILE, JR., M.D.

Dr. CRILE. Thank you, members of the committee, ladies and gentlemen.

Thirty years ago, if a woman had a lump in the breast there was no question. You saw the doctor, he said, "You have a lump and we will do the biopsy and, of course, if it's malignant we'll finish the operation," and that meant in the United States one thing. It meant the radical mastectomy. That has been described this morning eloquently. I do not need to go into the details of that.

Except to add one thing, and that is they did not speak about the adema of the arm, swelling of the arm, which is one of the most significant detrimental things which happens to the person after a radical mastectomy. In about 30 percent of the cases this happens. And this rises to 50 percent or more if radiation is added to the axilary dissection.

Now this, in 1950, this was still being done in the 1950's in the United States, routinely, although in England things were beginning to change. They had, indeed, changed since the 1930's when Sir Geoffrey Keynes began to do a little local excision of the tumor plus radiation, implants of radium seeds or specialized types of radiation to the tumor.

Reginald Murley, who since became the distinguished President of the Royal College of Surgeons in 1954, being an aggressive, young surgeon said "Keynes must be nuts to do these little operations," he had a long followup, 20 or more years on these people, and to his absolute astonishment he found that the patients who had the smaller operation had had just as good a survival rate, completely as good in every respect, as those treated contemporarily by colleagues of Keynes at the same time.

That's when McWhirter in Scotland started off doing the simple operations with radiation and Baclesse in France, doing the same

local excisions and irradiation, and Mustakalio in Finland. There was an outbreak of all that in the fifties. So, in 1955 I had gotten to know Reggie Murley well and he told me about all this and we decided there was no real excuse for routinely doing the radical.

We have done no radical mastectomies at the Cleveland Clinic since 1957. I changed in 1955 and did about 20 percent partial mastectomies, on the small tumors, with big-breasted women. Eighty percent were modified radicals or simples.

Now, radiation cannot be assumed to be, necessarily, a good thing to do routinely. Even in good hands it has side effects. It can change the skin, it can cause the breast to harden and be uncomfortable. It can cause hardening of the muscles so that it limits the motion. And it can cause swelling of the arm, especially if the axilla is dissected to remove the lymph nodes.

Well now, at the Cleveland Clinic today, and I think more and more throughout the country it's becoming this way, and there's a very important study by Fisher in his randomized group, coming out within the next few weeks, which I hope and believe probably will support this, because everything so far has, that there is no essential difference between the various methods of treatment of breast cancer, if you remove or destroy the local breast cancer. You may have a higher incidence of local recurrences because you may get new tumors in that breast, or you may get local recurrence of the old tumor if it hasn't been very widely excised. But these are almost invariably picked up very early, so their secondary treatment is highly successful.

Therefore, there is little or no difference in survival between these patients who have big operations or little operations.

I think that in small, peripheral—not near the nipple—apparently localized tumors, a partial mastectomy, removing a slice of breast like a piece of pie, reconstructing it, plus an axillary dissection is all that is needed. I think the axillary dissection should be done to sample the nodes and to see what, if any, further treatment may be necessary and also, because you're there and if you remove the nodes you avoid the necessity of subsequent operations if they do become involved.

Larger tumors or those near the nipple or not localized, can be treated by a so-called lumpectomy, which is not a very nice name, but it is a local excision, plus axillary dissection, and radiation, not to the axilla, but to the breast. We would never both dissect the axilla and radiate it, because that adds a double insult to the axillary lymphatics, which causes swelling of the arm.

And then in the large tumors, or when the nodes are clinically involved or the involvement is diffuse, then a modified radical mastectomy can be done with immediate reconstruction, and the immediate reconstruction has become extraordinarily successful. We are doing that routinely now and a modified radical today, or these with axillary dissection, means only 1 day of hospitalization. We can send the patients home with a drain and a special suction in, in 1 or at most 2 days. So, it's very economical.

There have been enormous advances in plastic surgery so that no woman today need live without a breast unless she wants to. And the decision as to which of these methods is something which you must discuss with the patient in long detail, let her make up her

mind which is most consistent with what is available to her in the form of radiation therapy treatment, and so forth, and what she wants to do.

Because, don't forget, radiation therapy is costly. It takes 5 weeks. And it can cause side effects.

Now, on chemotherapy I am going to speak to shortly. It delays appearance of recurrences certainly. Maybe it increases survival. Premenopausal women are the ones that get the benefits, though, so the question is whether it does this through the endocrine system.

The British oncologists think that it does, that its effect mainly is through the endocrine system and in the long run treatment may be just as effective if we treat these patients with tamoxifen, the antiestrogen, and various sterilizing procedures, as with the costly and very unpleasant side effects of chemotherapy.

So, the history of breast cancer has been that of excess, first in surgery then in radiation, now perhaps in chemotherapy. We don't know.

Diagnosis: The woman has nerves both in the breast and in her fingers. A mammogram can show calcium early. Maybe you could have one at 40, 45, and 50. Then every 2 years after that. But this is very costly. We should talk about cost effectiveness.

Now, in the history of breast surgery, it's been to the interest of physicians, to promote radical treatments. The trouble is worse now because we're getting a threat by law that if we don't do radical things, if we omit something, we may get a suit. And that's a very grave thing.

Cost effectiveness——

Ms. OAKAR. On that note—that's very interesting to this committee, about the threat of suits if you don't do the radical and all that, and your pioneer work in this effort.

We have a vote. We'll be right back.

So, we'll just recess for a few minutes.

[Brief recess.]

Ms. OAKAR. Dr. Crile, I didn't mean to interrupt your statement.

Dr. CRILE. You couldn't help it.

Ms. OAKAR. Will you please resume and then we'll hear from our other witnesses?

Dr. CRILE. Sure.

I was speaking about the cost effectiveness of mammography, because this has not been, yet, clearly established. It has been established that in premenopausal women it is not as effective as it is in postmenopausal women, but exactly how often this should be done at the present expense of mammography is a question.

The other possibility is could the cost of mammography be reduced by having screening examinations done by nonmedical personnel, highly trained technologists, who would take a single lateral picture, examine the breast, and that would be that? And I would think that you could cut that down and massproduce that and in some way do it.

The other thing in diagnosis is aspiration, which is not as widely used as it should be. Still, a lot of patients go to surgery without having had aspiration of the mass, with an established diagnosis. That means an open biopsy has to be done instead of a little office

procedure. The cost is much more. The patient has a complete cure, if it's a cyst, and doesn't need any operation.

Ms. OAKAR. What does an aspiration do?

Dr. CRILE. An aspiration is merely putting a fine needle in the office, freezing the skin so it doesn't hurt, or just needling it with a very fine needle, very little discomfort at all, and if it's a cyst, the patient is cured and lives happily ever after. You don't have to worry about it.

So, it's just not done enough. You still see cysts that are removed surgically. That's because they are not being aspirated in the office.

A summary of the history of breast cancer has been a series of controversies and one of the problems has been that it's to the interest of the fee for service physicians to promote larger operations. I don't think they should be paid more for a large operation than for a small. That's been bad.

Chemotherapy has been extended over a very long time, whereas there's no indication that it needs more than a few months. And frequent mammography has been advised sometimes as often as every 6 months, whereas you have to have cost-effective studies to determine its value.

And, of course, the other thing which is driving us toward more radical and more frequent operations is the malpractice threat, which is higher in this country than anywhere. That's probably why most of the simplifications of the treatment of breast cancer have come from elsewhere rather than from the United States.

So, in conclusion, I think that we're headed toward a varied approach to breast cancer, in which the treatment selected will depend on the size and position of the tumor. Also, of course, on the size of the breast because a small tumor in a small breast is OK but a big tumor in a small breast cannot be treated by anything that's going to preserve much breast, unless you use a lot of radiation.

And finally, cost effectiveness of all of these things must be worked out, and it's hoped that something can be done to diminish the harm that malpractice suits are doing to the cost and to the quality of medical care.

Ms. OAKAR. Well, thank you very much, Dr. Crile, and we're going to have questions in a few minutes for both of you.

Our next witness is Dr. Barbara Threatt. Did I pronounce your name correctly?

Dr. THREATT. Yes.

Ms. OAKAR. Thank you very much for being here, Doctor.

[The prepared statement of Dr. Crile follows]:

PREPARED STATEMENT OF GEORGE CRILE, JR., M.D.

HISTORY OF BREAST SURGERY

Thirty years ago, there were no arguments about the diagnosis and treatment of cancer of the breast. A lump was felt and the patient was told that a biopsy must be taken, and that if the biopsy showed cancer "the operation would be completed". That meant a Halsted type of radical mastectomy with removal of the muscles of the chest wall and often with removal of so much skin that grafts were required. Often, even in patients with small tumors, radiation was added.

The results were appalling. Not only was the chest wall disfigured by paper thin skin flaps that lay on the bare ribs, but also there often was limitation of the motion of the shoulder. In thirty percent of the cases, and in 50%, when radiation

was given, there was swelling of the arm, sometimes massive and incapacitating. That was in America where the radical mastectomy had been popularized by Dr. Halsted.

In England, where in 1867 the radical operation had been devised by Charles Moore, most surgeons were still doing it. But in the 1930's Sir Geoffrey Keynes began to use a combination of local excision and radiation and did no radical mastectomies. In 1954 a friend of mine, Reginald Murley, who was a surgeon at St. Bartholomew's Hospital, began to study the results of Keynes' operations in hopes of showing the failure of local excisions. To Murley's amazement, Keynes' patients had just as good a long-term survival as those treated by Keynes' colleagues who had done radical mastectomies. By this time, Keynes' work also had stimulated McWhirter in Scotland, to treat patients by simple mastectomy and radiation. The results of this combination were as good as those following radical mastectomy. At about the same time Baclesse in France and Mustakallio in Finland reported similar success following radiation associated with local excisions that preserved the breast.

By 1955 it was obvious that surgery or radiation or any combination of the two that destroyed the local tumor and its metastases to the nodes in the axilla was as effective as the most radical operation. Therefore, after a long talk with Murley, I stopped doing radical mastectomies and switched mainly to modified radicals in which the muscles were preserved but the axillary nodes were removed. In 15 to 20% of the cases the tumors were small in relation to the size of the breast and were located in the periphery so that the segment of the breast could be removed and the breast reconstructed. These tumors were treated by wide excision, which we called partial mastectomy. We have followed more than 200 of these patients for 10 to 20 years. Although there is a slightly higher incidence of local recurrences and new tumors appearing in the affected breast, the survival rate is the same as in patients with similar tumors treated by radical operations.

THE PRESENT STATUS OF KNOWLEDGE

At the present time large randomized trials have shown that, in patients with tumors that are small in relation to the size of the breast, local excision, and expertly given radiation give results that in terms of both local recurrence and survival are equal to those that follow radical mastectomy. The problem is that radiation, in the doses required to give these results, can cause side effects such as skin changes, shrinking of the breast and swelling of the arm. It also has been shown in randomized trials, that adding radiation to radical or modified radical mastectomy does not increase survival, and there is the remote possibility of the radiation proving carcinogenic by scatter to the opposite breasts or to the underlying tissues. Also from the standpoint of both time and economy, radiation, which takes about 5 weeks, is costly. Hence, in selected cases, methods that do not require radiation may be preferable.

Partial mastectomy, which involves a wider removal of breast tissue than mere local excision of the tumor, is always combined with axillary dissection and in about 20% of the cases can be used as the only treatment for small apparently localized cancers. In selected cases we have been using this treatment for nearly 30 years and are convinced that from the standpoint of survival it is as effective as either radical mastectomy or lumpectomy and radiation. This opinion has not yet been confirmed by a randomized study, but within the next few weeks such a study will be published by Dr. Fisher and his surgical adjuvant group. If it shows what I expect, the treatment of breast cancer will become selective, with the treatment adapted to the individual.

1. Small peripheral tumors that appear to be localized will be treated by partial mastectomy and axillary dissection. This effects an enormous economy, because it involves only a day or two of hospitalization and radiation is not required.

2. Tumors that are located near the nipple or that are not sharply localized in the breast or that are large in relation to the size of the breast will be treated by local excision (lumpectomy), axillary dissection and radiation to the breast but not to the axilla.

3. Larger tumors or those with obvious involvement of nodes or with multiple foci of cancer in the breast will be treated by modified radical mastectomy with radiation. In these cases the breast can be reconstructed by plastic surgery. In short, no woman need live without a breast unless she prefers to do so.

ADJUVANT THERAPY

Adjuvant chemotherapy delays the time of reappearance of breast cancer. It is possible that chemotherapy also increases the long-term survival. However, it is chiefly the premenopausal patients that benefit from chemotherapy, a fact that suggests that the effect of the treatment is not a direct one on the cancer cell. It seems more likely that chemotherapy acts indirectly by suppressing the output of the estrogen that stimulates the growth of breast cancer. Since removing the ovaries or radiating them or giving the anti-estrogen drug tamoxifen also slows the growth of the cancer and in controlled studies has been shown to increase the patient's survival, we are awaiting the results of controlled trials of chemotherapy vs. anti-estrogens. I agree with most of the British oncologists who think that the anti-estrogens therapy will prove to be as effective as chemotherapy.

The side effects of anti-estrogens are minimal as compared to the nausea, vomiting and loss of hair that result from chemotherapy and the cost is much less.

It seems that in the treatment of breast cancer we always go to excesses. First, it was too much surgery, next too much radiation and now, perhaps, it is too much chemotherapy.

DIAGNOSIS

Since a woman, examining her breast, can feel a tumor not only through the nerves in her fingers but also through those in her breast, self-examination remains the most effective low-cost way of detecting early cancers. Mammograms, however, can detect them even earlier, before they are large enough to feel. The question is at what age and how often should mammograms be done. The trouble is that, when used for screening population groups, mammograms are so costly that their frequent use is not cost-effective. Also, they are not effective in showing small tumors in the firm dense breasts of premenopausal women. Most studies of the cost-efficacy of mammography in saving lives conclude that base line mammograms should be done at ages 40, 45, and 50. Also women with a history of breast cancer or those with a strong family history should have annual mammograms and women after the age of 50 should have them at least every two or three years.

Most breast lumps should be diagnosed in the office by fine-needle biopsy. If they are cysts, removal of the fluid cures them. If they are solid tumors the aspiration biopsy tells if thye are benign or malignant. This saves the hospitalization and costly preparation for major surgery that takes place if the patient is admitted for open biopsy and definitive surgery.

CONCLUSION

The history of cancer of the breast has been a series of controversies. In the United States, it has been to the interest of the physician to promote radical operations, prolonged chemotherapy, and frequent mammograms. Not only does this increase the practice of the physician, but it also protects him against the possibility of malpractice suits.

If a surgeon, in America fails to do the radical operations that are in vogue and if the patient is not cured, the surgeon can be accused of negligence. The same applies to radiation therapy and to mammograms. Perhaps that is why all of the leaders in the simplification of the treatment of breast cancer have lived in England, France or Scandinavia.

STATEMENT OF BARBARA THREATT, M.D.

Dr. THREATT. Ms. Oakar, ladies and gentlemen, I appreciate the opportunity to discuss the matter of breast cancer with you this morning. It is certainly a significant event that you, as policymakers, are directing your attention to this matter. I hope the data we provide will aid you in your decisions.

Breast cancer, as you have heard, is the No. 1 cancer problem for the American female, with a mortality rate that is unchanged over the last 50 years. There's been no real change. This is undoubtedly due to the fact that of the late stage at which the cancer is diagnosed, there has been no real change in the staging of the breast cancer over this time period.

Ancillary treatment, such as radiation and chemotherapy, can at best serve only as a palliative or delaying treatment in such a situation. In order to improve the survival from breast cancer, the stage of the disease at the time of diagnosis must be changed. To accomplish such a change in the stage of the disease requires a change in our efforts concerning this disease. We must direct our attention to the asymptomatic woman and screen her for the possible occult breast cancer that she may have. In this way smaller cancers with a lower incidence of positive lymph nodes will be detected. Survival will be improved as the stage of the disease at diagnosis is decreased.

The Swedish breast cancer incidence, the mortality data, provide an example of this hypothesis. The incidence of breast cancer in Sweden is quite similar to that in the United States. But because many more cancers are detected at a smaller size, around 1 centimeter or so, the mortality rate is 25 percent less than in the United States.

Unless there is a change in the staging of the cancer at the time of diagnosis, it is unrealistic to expect a change in our mortality rates. There is little likelihood that therapeutic efforts, directed toward a system disease such as breast cancer, will be able to increase survival.

There seems to be little——

Ms. OAKAR. I'm sorry, Doctor. It is a systemic disease?

Dr. THREATT. Absolutely. And from probably the time of diagnosis, if not before.

Ms. OAKAR. But we don't treat it that way, do we?

Dr. THREATT. That's right.

Ms. OAKAR. OK.

Dr. THREATT. Not until the metastases become obvious.

Ms. OAKAR. Aha.

Dr. THREATT. There seems to be little attention paid to breast screening from the medical profession or from the women themselves. According to the National Center for Health Statistics, in 1973 only 45 percent of the 45- to 64-year-old women had had a breast examination in the previous year, and only 29 percent of the 65-year-old women had had a breast physical examination in the previous year.

In 1979, the percentage had increased to approximately 59 percent of the 45- to 64-year-old women having a breast physical exam within the previous year.

Data concerning utilization of mammography is even more dismal. Data from the Office of Cancer Communications national survey shows that only 19 percent of all American women have ever had a mammogram.

FDA data records show that 2 million mammograms were performed in 1980. This documents gross underutilization of the techniques since there are 34 million women in this country over 50 years of age, and 12 million between 40 and 49.

The problem of breast cancer is a complex one which must be addressed on many levels, basic research, detection, diagnosis, management, professional, and public education, et cetera.

My recommendations for addressing this problem would include the following: Women over 40 years of age should be screened for

breast cancer on a regular basis, including physical examination and mammography. Probably on an annual basis. Perhaps it could be extended to 18 to 24 months for some women.

The need for this routine screening does increase with the age of the woman. Screening should be accomplished at breast cancer detection centers staffed by experts in mammography and breast disease. The centers should function not only for screening but for the diagnosis and management of breast disease.

Radiologists who interpret mammograms should be especially trained and certified, not only in an interpretation of the mammograms, but in the diagnosis and management of all breast disease, including cancer. Technologists who perform mammograms should also be trained and certified.

The equipment utilized for mammography should be state of the art and appropriate for the technique, whether film or xerography is used.

Regular monitoring of the radiographic equipment and patient dose should be carried out by physicists.

Pathologists involved in the diagnosis of breast cancer should have expertise in breast pathology. This is especially important for the diagnosis of small cancers and the atypical benign diseases.

An interdisciplinary team should determine the treatment and management of the breast cancer patient. This is important to assure that all options for treatment are considered and explained to the patient. There should be a commitment to breast conservation, where it is possible as a therapy.

Results of the screening should be carefully monitored concerning radiation dose levels, mode of cancer detection, size of cancer detected, nodal status, biopsy rate, and biopsy yield.

If there is no change in the type of cancers detected by the centers, from those detected in the clinically symptomatic population, careful reevaluation of the type of population served, asymptomatic versus symptomatic, should be carried out.

A screening program evaluating asymptomatic women should find significantly smaller, less node positive cancers than are found in the clinically symptomatic population. Long-term followup for the breast cancer patient should be carried out. This should include psychosocial support for the patient and her family, as well as data collection.

There should be a commitment to public and patient education concerning these matters, especially as to the benefit of screeners.

Cost of the screening should rest with the health coverage provider, the women, and the providers of the service. The health coverage providers, essentially the insurance companies, should carefully evaluate the data concerning the cost benefit of screening and consider some provision for covering this service, this type of screening.

The physicians involved should consider innovative ways of providing low cost breast cancer screening, and the women themselves should be willing to assume some of the costs of their own health care.

Mammography is the only screening procedure which has been shown to save lives. It is a valuable and powerful resource which could effectively change the breast cancer mortality rate in this

country, if effectively utilized. It is our duty to assess this situation and find a practical, workable way to deliver this life-saving procedure to our at-risk female population.

[The prepared statement of Dr. Threatt follows:]

PREPARED STATEMENT OF BARBARA THREATT, MD [1]

BREAST CANCER IN THE UNITED STATES, 1984

Breast Cancer is the number one cancer by incidence in the American female population with 115,000 new cases predicted to occur in 1984 by the American Cancer Society. Breast cancer is similarly the prime cause of cancer deaths in the American female population with 37,300 predicted deaths in 1984.

This is a staggering toll of lives and anguish for the female population and is a major public health problem for this country. Furthermore, the death rate from breast cancer has remained unchanged for the last 50 years at approximately 25/100,000 women per year. Since there has been a slow increase in incidence rate over this time period (from 1 in 15 women in the past having the disease to our current 1 in 11 having the disease), the death rate could actually be somewhat improved but masked because of the increased numbers of women presenting with the disease. In any event, the disease represents a serious public health problem for this country, as well as for individual women.

Approximately $575 million will be spent in the United States this year for 115,000 mastectomies and approximately $1,150,000,000 will be spent for about one million breast biopsies. These figures do not include the cost of radiation treatment, chemotherapy, diagnostic test, or loss of wages. These figures do serve, however, to delineate somewhat the scope of the breast cancer problem in our population.

Currently, little is known about the eitiology of breast cancer. Many isolated facts and associated risks for breast cancer can be identified, but no cohesive, cogent theory of etiology is available. Many factors, such as age, pregnancy history; menstrual status, family history of breast cancer, and previous breast biopsy, can be identified as significant risk factors for the development of breast cancer. However, none of these risk factors is strong enough singly or grouped to serve to identify a "high risk" woman. As Seidman pointed out in CA (September 1982), "any woman 40 years or older must be considered at significant risk of having or developing a breast cancer."

Since there is little information concerning the basic etiology of breast cancer, primary prevention is not possible at this time. Survival from breast cancer has been shown to be related to the state of the disease at the time of diagnosis. Staging depends upon the size of the cancer in the breast and the status of the axillary lymph nodes. Small size of the cancer and negative axillary lymph nodes have the best prognosis for long-term survival.

Currently, approximately 50% of white women and 61% of black women with breast cancer have positive lymph nodes at the time of diagnosis (Table 1). These are dire implications for survival as shown in Table 2, with approximately 73% of the women surviving five years if the cancer is limited to the breast. Survival decreases significantly as the disease progresses to regional and distant lymph nodes. Overall, the best indicator for survival is the status of the axillary lymph nodes as shown in Table 3. the size of the cancer is intimately related to the number of positive lymph nodes as shown in Table 4. Survival decreases significantly with each additional positive lymph node. The figures in these tables from the American College of Surgeons' 1977 survey of hospital cancer registries are dismal, and is little different from the more recent 1981 (unpublished as yet) survey. These survival figures at five years post-diagnosis give only partial information; the survival figures at 10 years post-diagnosis are the more informative and give a better estimate of the true survival picture. Survival at 10 years for a lymph node negative breast cancer patient is approximately 60-70%; for a woman with 1-3 positive lymph nodes, it is 45%, and for a woman with 4 or more positive lymph nodes, it is only 20%.

From these facts and figures, it can be seen that survival, size of the cancer, and extent of the disease (local, regional, or distant) are intimately related. Survival is best if the cancer is detected at a small size (certainly less than 2 cms) and if the regional (axillary) lymph nodes are negative.

---

[1] Director, Detection and Prevention Services, Michigan Cancer Foundation, Detroit, MI (formerly Associate Professor of Radiology, The University of Michigan and Director of the University of Michigan Breast Cancer Detection Demonstration Project).

Today, approximately 75-90% of breast cancers are detected by the woman herself. There is considerable controversy about the efficacy of breast self-examination (BSE), but nevertheless, the individual woman currently serves as her own diagnostician in detecting breast cancer. Tables from the American College of Surgeons' 1977 survey of Hospital Cancer Registries illustrate some aspects of this problem. In Table 5, it can be seen that young women tend to discover more of their breast cancer than older women, suggesting that the practice of BSE is age related. In Table 6, it is shown that the size of the tumor is related to the mode of detection, with those found by mammography being the smallest. In Table 7, nodal status is compared with mode of detection; in those women whose cancers were detected by mammography, 73% had negative lymph nodes compared with 58% in the patient-detected group and 63% in the physician-detected group.

Detection of breast cancer at the smallest possible size is our current focus in cancer control since primary prevention is not feasible given our lack of understanding of the basic etiology of breast cancer. The available techniques for detection of breast cancer include the following:

1. Breast Self Examination (BSE): Considerable controversy exists about the teaching, practice, and efficacy of BSE. No randomized controlled clinical trial has ever been carried out to assess BSE and it is unlikely to be carried out. It is probable that BSE could and does contribute to the detection of breast cancer; whether it can contribute to the detection of small, curable breast cancer is open to question.

2. Clinical Physical Examination of the Breast: This technique is the predominant technique used in breast evaluation. No true trial of clinical examination has been carried out, although data from the May Clinic (Gilbertsen) covering 1948-72 and 9,289 women with 51,398 examinations showed routine examinations had only 56% true-positive rate in finding breast cancer. In the Breast Cancer Detection Demonstration Projects (BCDDP), physicial examination alone detected only 13% of the cancers in the under 50 year old women category and 56% of the cancers in the over 50 year old women category. It was able to detect 38.5% of the non-invasive cancers and 44.4% of the less than 1 cm invasive cancers in BCDDP. There are, therefore, significant questions as to the efficacy of physical examination in the detection of small, curable breast cancers.

3. Mammography: This technique of soft-tissue radiography of the breast was introduced by Egan in 1960. The technique has undergone significant modifications over the last 20 years with the introduction of new film, screens, and special dedicated mammographic units. The radiation dose currently required for "state-of-the-art" film mammography is extremely low and reproducible. BCDDP mammography alone detected 35% of the cancers in the under 50 year old woman category. Totally, mammography detected 85.4% of the cancers in the under 50 year old women and 91.8% of the cancers in the over 50 year old women category (Table 8). Mammography detected 92% of the non-invasive cancers and 89% of the under 1 cm invasive cancers (Table 9). Concern has been raised, however, regarding the carcinogenic risk of mammography, especially in an asymptomatic population. However, with proper utilization of currently available techniques, there is very little risk to the 40+ year-old women from radiation required for these tests.

4. Thermography: This involves measurements of infrared radiation from the breasts. This technique has been widely publicized as a screening and diagnostic test for breast cancer. Reports concerning its efficacy in the medical literature vary widely. Currently, it is not widely used because of the lack of efficacy in detecting small cancers and a high number of false-positives.

5. Ultrasonography: This is an experimental technique which may have some efficacy in special groups of women, i.e., young women or those with dense breasts on the mammogram. Much controversy exists about its accuracy and resolution and its place in the spectrum of breast examination modalities. Currently, it seems to be best used to discriminate a solid from cystic mass. It should not be used as a screening test since its efficacy as a diagnostic test has not been established. It is hoped that further improvements in its resolution will enhance its ability to detect small (under 1 cm) cancers.

6. Diaphonography, Transillumination, Lightscanning: These are various techniques using infra-red light transmission through the breasts. They measure the transmitted light and record changes in the color of the transmitted light and relate this to normal, benign, or malignant abnormalities. Currently, these seem to have little efficacy and offer little improvement in diagnostic capability over that of a combined physical examination and mammogram. However, they are interesting tests since, as in ultrasound, no radiation exposure is required for the patient.

7. Nuclear Magnetic Resonances: An experimental technique using large electromagnets to measure changes in cellular structures. This is truly in an experimental

stage so that little is known about its capabilities. It offers promise as a nonionizing procedure and potentially as a dynamic evaluation of the cellular and molecular structures of the breast.

The above techniques are our armamentarium for breast examinations. There are no other tests for the status of the breast other than surgical biopsy. Unfortunately, there is no blood, urine or skin test to serve as a marker or identifier of the woman with breast cancer. No such test is even promised for the near future. We are, therefore, left with our older techniques which, with the exception of mammography, are inefficient for the detection of small, potentially curable breast cancer.

Several screening programs have been established around the world. The major ones and their goals and results are listed below:

1. The Health Insurance Plan of New York (HIP) Study conducted from 1963-1968. This was a large-scaled randomized controlled clinical trial of 61,000 women to determine if screening by physical examination and mammography could decrease mortality from breast cancer. The results clearly showed at least a 30% reduction in mortality in the short and intermediate term (3-12 years); however, this benefit was limited to the over-50-year-old women. It seems from current studies in BCDDP that the lack of benefit for the under 50-year-old women may have been due to the less technologically advanced mammographic techniques available during the time of the HIP Study and not to an inherent difference in cancer type and survival in the under-50-year-old women.

2. The Breast Cancer Detection Demonstration Project (BCDDP) was conducted by the National Cancer Institute/American Cancer Society from 1973-1980. This was a demonstration project in which 280,000 women were screened annually to show that physical examination and mammography could detect "early" (small, less lethal) cancers in asymptomatic women. The results of this program clearly demonstrate that small cancers with no positive lymph nodes can be detected in an asymptomatic population, in both the under 50 and over 50 year old women categories. The prime mode of cancer detection in this program was by mammography; this was especially true for the small cancers. Detection was accomplished using extremely low radiation levels. Unfortunately, no control population was included in the design of the study, so survival/mortality data are not available for this project.

3. Other screening programs have been designed and are currently underway in Europe (Table 10). These have various designs for the control populations, physical examiners, and interpreters of the mammograms.

4. A Canadian trial is also underway in several locations. This is under the direction of Dr. Anthony Miller, but final data are not yet available from this study.

There has been considerable concern expressed about the possible carcinogenic effect of mammography. These concerns derive from data showing an excess incidence of breast cancer in several groups of women exposed to high doses of radiation when these were compared with similar population of nonexposed women. These groups were:

1. Japanese women exposed to gamma and neutron radiation from atomic bombings at Hiroshima and Nagasaki.
2. Nova Scotia sanitaria patients who received multiple chest fluoroscopes during pneumothorax treatment for tuberculosis.
3. Massachusetts sanitaria patients monitored by fluoroscopy during artificial pneumothroax treatment.
4. Women treated by radiotherapy for post-partum mastitis in Rochester, New York.
5. Swedish women who received radiation therapy for a variety of benign breast conditions.
6. Female radium dial workers who ingested radioactive material from their work.

Whether the very low doses of radiation used for current mammographic techniques can produce breast cancer is unknown. If the risk is real, it is so small that it has been unobserved in collected medical data. The possibility of such a risk has only been inferred from the excess in number of cases identified in those groups of women exposed to high doses of radiation.

The effects of low doses of radiation can be postulated from animal experiments involving several radiation induced tumors. The dose response curve is linear in the mid-portion of the curve but curvilinear in the lower dose range. There is less effect at high doses due to cell death.

There is considerable controversy as to whether the results from the animal experiments are applicable to humans. The data from the groups of women exposed to high levels of radiation who subsequently developed carcinoma are similar in many respects to the results of the animal studies. However, the data for lower levels of

radiation (25-50 rads) exposure to women are incomplete. It is impossible to determine whether the doses response at these low levels is a linear or curvilinear response. If the response is curvilinear, the linear projections significantly overestimate the levels of risk. The Committee on the Biological Effects of Ionizing Radiation (BEIR) III report has employed a combined linear-quadratic model for human cancers. This report states, however, that it is unknown whether human breast cancer follows the pattern set by most other human and animal cancers at low doses levels or whether it is an exception with a linear response down to 0 rads. The projected risk for the three groups of Western women studied is 7.5 excess cancers/million women/year/rad. This risk is a linear extrapolation from high doses and is made in the absence of any significant low-dose human breast cancer data. This estimate is probably a substantial overestimate of the risk and should be considered the upper limits of the risk.

Radiation risk is not only dose dependent but is highly dependent on age at time of exposure. In all studies, the risk is significantly greater with radiation exposure at younger ages. No excess risk was found in Japanese women 20 years or older at time of exposure to 100 rads or less. For this reason, the National Cancer Institute (Upton, et al., 1977) projected a risk adjustment factor of 0.45 for Western women over 30 years of age; this reduces the projected risk from 7.5 to 3.5 excess cancer/million women/year/rad for Western women over 30 years at time of exposure.

There is also a latent period associated with the carcinogenic effect of radiation upon the human breast. These cancers do not appear for a minimum of 10 years following exposure. For younger women at the time of exposure, the latent period is even longer, varying from 15-20 years. The duration of the carcinogenic effect is unknown, but it certainly persists for at least 15 years.

This risk estimate of 3.5 cancers/million women/year/rad means that if a million women receive a mean breast dose of 1 rad, there would be an excess incidence of 3.5 breast cancers each year in the population after a minimum latent period of 10 years. Mammograms performed utilizing the currently low-dose film technique of 0.17 rad mean breast dose, would carry a possible risk of one excess cancer case/year/2 million women examined. Assuming a 50% mortality rate, this would equate with one excess death/4 million women examined. The projected risks from mammography, therefore, is extremely small compared with that from natural breast cancer incidence: 800 cases/million women/year at 40 years; 1,800 cases/million women/year at 50 years; 2,500 cases/million women/year at 65 years.

The risks of low-dose mammography have not been proved or disproved. It is prudent, however, to assume that such a risk exists and to assure that the lowest possible radiation dose is used to obtain optimum film quality.

The HIP Study has shown definite survival benfits for over 50 year old women who were screened by physical examination and mammography. Data concerning benefits of screening in the under 50 year old women will be derived from the controlled trails in Sweden and Canada; however, such data are not currently available. It is reasonable, however, to assume that such benefit will be shown considering the advances in mammographic techniques and the differences in size and nodal status of the tumor detected in the screened groups. Table 11 (Feig, 1984) demonstrates estimates of the benefits and costs of screening covering years gained or lost by age group undergoing mammographic screening. The projected benefits of mammographic screening outweighs the risks at all ages.

The above data clearly show that breast cancer is the number one cancer problem for the American female and that the mortality rate is unchanged over the last 50 years. This is undoubtedly due to the late stage at which the cancer is diagnosed. There has been no real change in the staging of breast cancer over this time period. Ancillary treatment (radiation and chemotherapy) can at best serve as delaying or palliative treatment in such a situation. In order to improve the survival from breast cancer, the stage of the disease at diagnosis must be changed. To accomplish such a change in the stage of the disease requires a change in our efforts concerning this desease. We must direct out attention to the asymptomatic woman and screen her for the possible occult breast cancer that she may have. In this way, smaller cancers with a lower incidence of positive lymph nodes will be detected. Survival will be improved as the stage of the disease at diagnosis is decreased. Swedish breast cancer incidence and mortality data provide an example of this hypothesis. The incidence of breast cancer in Sweden is similar to that of the United States, but because far more cancers are detected at a smaller size (about 1 cm), the mortality rate is 25% less (18/100,000 as compared whith 25/100,000). Unless there is a change in the staging of the cancer at the time of diagnosis, it is unrealistic to expect a change in our mortality data. There is little likelihood that therapeutic effort directed toward a systemic disease such as breast cancer will be able to increase survival rates.

Currently in this country, the majority of women are screened annually by a Pap smear for cervical cancer. Cervical cancer has a low incidence and low mortality rate in our female population, especially in the middle and upper socioeconomic group women who tend to receive the majority of the Pap smears. As can be seen from Figures 1-4, the incidence of cervical cancer is quite low in comparison to that of breast cancer, and, even in relationship to that of ovarian and uterine cancer. The mortality data are even more striking; the mortality of breast cancer far outweighs that of even the combined mortality of all genital cancers. Breast cancer mortality is greatly in excess of that of cervical cancer; mortality from ovarian and uterine cancer greatly exceeds that of cervical cancer.

These data are striking in contrast to the type of screening examination that most women receive, i.e., a cervical Pap smear. There seems to be little attention paid to breast screening from the medical profession. According to the National Center for Health Statistics, in 1973 only 48% of the 45-64 year old women had had a breast physical examination within the previous year and only 29% of the 65+ year old women had had a breast physical examination within the previous year. The National Center for Health Statistics, in a telephone survey in 1979, found that 59% of the 45-64 year old women had had a breast physical examination within one year; but this may be an overestimate of the number of women actually receiving the examination. Data concerning utilization of mammography are even more dismal. Data from the Office of Cancer Communication's national survey show that only approximately 19% of American women overall have ever had a mammogram. It is also probable that utilization of mammography is greater for the under 50 year old women in whom the cancer risk is less but in whom painful masses may be present. FDA data records show that two million mammograms were performed in 1980. This shows gross under-utilization of the technique and raises questions as to the validity of the data showing 19% of all women had ever received a mammogram.

Several studies (Battista, 1983; Cummings, et al., 1983; McDonald, et al., 1984) have pointed out the physicians rarely order mammography, and that this is especially true in the case of the asymptomatic woman. These same physicians also state that mammography is the most effective method of detecting small cancers. Their stated reasons for not using mammography were perceived ineffectiveness and unreliability of the procedure, low prevalence of breast cancer, radiation risk to the patient, and cost. The radiation risk concern should not be a deterrent to the use of modern mammographic techniques and can be addessed through physician education. The other concerns may be more complicated and may not really address the real reason for the lack of screening. Since clinical physical examination of the breast apparently is performed infrequently, even in the age group at most risk for developing breast cancer, and physical examination carries no perceived risk, it seems that other factors than cost, radiation risk, questions of reliability, etc., may be playing a role in the utilization of both mammography and physical examination.

The problem of breast cancer is a complex one which should be addressed on many levels, i.e., basic research, detection and diagnosis, management, professional and public education, etc. My recommendations for addressing this problem would include the following:

1. Women over 40 years of age should be screened for breast cancer on a regular basis, probably at annual or no longer than 18-24 month intervals. The need for this routine screening increases with the age of the woman.

2. Screening should be accomplished at Breast Cancer Detection Centers staffed by experts in mammography and breast diseases. The Centers should function not only for screening but for diagnosis and management of breast diseases.

3. Radiologists who interpret mammograms should be specially trained and certified, not only in interpretation of mammograms but in diagnosis and management of all breast diseases and problems. Technologists who perform mammograms should also be specially trained and certified.

4. The equipment utilized for mammography should be "state-of-the-art" and appropriate for the technique (film or xerography) used.

5. Regular monitoring of the radiographic equipment and patient dose should be carried out by physicists or physics centers.

6. Pathologists involved with the Centers should have special expertise in breast pathology. This is especially important for the diagnosis of small cancers and the atypical benign diseases.

7. An interdisciplinary team should determine the treatment and management of the breast cancer patient. This is important to assure that all options for treatment are considered and explained to the patient. There should be a commitment to breast conservation where it is possible as a therapy.

8. Results of the screenings should be carefully monitored concerning radiation dose levels, mode of cancer detection, size of cancers detected, nodal status, biopsy rates and biopsy yields. If there is no change in the type of cancers detected by the Centers from those detected in the clinically symptomatic population, a careful re-evaluation of the type of population served (asymptomatic or symptomatic), techniques, level of expertise of the mammographer, and biopsy rates should be carried out. A screening program evaluating asymptomatic women should find significantly smaller, less node positive cancers than are found in the clinically symptomatic population.

9. Long-term follow-up of breast cancer patients should be carried out. This should include psychosocial support for the patient and her family, as well as data collection.

10. There should be a commitment to public and patient education concerning these matters, especially as to the benefit of screening.

11. Cost of the screening should rest with the health coverage providers, the women, and the providers of the service. The health coverage providers (insurance companies) should carefully evaluate the data concerning the cost/benefit of screening and consider some provision for covering this type of screening. The physicians involved should consider innovative ways of providing low-cost breast cancer screening. The women should be willing to assume some of the cost for their own health care.

Mammography is the only screening procedure which has been shown to save lives. It is a valuable resource which could effectively change the breast cancer mortality rate in this country if effectively utilized. It is our duty to assess this situation and find a practical, workable way to deliver this life-saving procedure to our at-risk female population.

Table 1. Distribution by Race and Clinical Stage

	White		Black	
	No.	%	No.	%
Localized	10,681	51.4	709	38.7
Regional to adjacent tissue	828	4.0	96	4.8
Regional to axillary nodes	6,437	31.0	657	33.1
Regional to adjacent tissue and axillary nodes	1,513	7.3	217	10.9
Distant	1,324	6.3	249	12.5
All stages	20,783	100.0	1,988	100.0

Table 2. Five Year Survival and Cure Rates by Race and Clinical Stage

	[redacted]		Black	
	Survival	Cure	Survival	Cure
	%		%	
Localized	73.0	60.7	70.8	57.1
Regional to adjacent tissue	49.5	38.4	42.7	29.2
Regional to axillary nodes	53.3	37.4	44.0	29.7
Regional to adjacent tissue and axillary nodes	37.3	22.4	20.8	13.4
Distant	10.9	3.2	5.6	1.6
All stages	59.3	46.1	46.9	35.0

SOURCE: Nemoto, et al., "Female Breast Cancer: A National Survey," Cancer, (June 15, 1980), p. 2920.

Table 3. Five Year End Results (Absolute Survival, Cure and Recurrence Rates) in 20,547 Patients of Breast Cancer in Females According to Number of Pathologically Positive Axillary Nodes

Number of positive axillary lymph nodes	Total Observed	Survival	Cure	Recurrence
0	12,299	71.8	59.7	19.4
1	2,012	63.1	48.4	32.9
2	1,338	62.2	45.4	39.9
3	842	58.8	39.3	43.0
4	615	51.9	38.4	43.9
5	478	46.9	29.1	54.2
6-10	1,261	40.7	23.0	63.4
11-15	562	29.4	14.8	71.5
16-20	301	28.9	13.3	75.1
21+	225	22.2	9.8	82.2
All nodes or some nodes positive	614	40.4	26.9	58.6
Total, positive nodes	8,248	50.9	35.0	49.2

Table 4. Percent Distribution by Race, Tumor Size and Nodal Status

	White		Black	
	Negative nodes	Positive nodes	Negative nodes	Positive nodes
0.1-1.0 cm	9.9	4.0	6.4	1.0
1.1-3.0 cm	55.2	39.6	45.4	26.0
3.1-5.0 cm	16.4	20.7	23.9	24.9
5.1+ cm	4.6	9.0	11.2	20.6
Unknown	13.9	26.7	13.1	27.5
Percent	100.0	100.0	100.0	100.0
TOTAL	7733	6245	551	659

SOURCE: Nemoto, et al., "Female Breast Cancer: A National Survey," Cancer, (June 15, 1980), pp. 2920-2921.

Table 5. Analysis by Age Group

Age at Admission	Tumor Discovered By: Patient No.	Patient %	Physician No.	Physician %	Mammography No.	Mammography %	Total No.	Total %
Less than 45	1407	80.4	291	16.6	52	3.0	1750	100.0
45-49	1019	75.9	263	19.6	60	4.5	1342	100.0
50-54	1132	74.7	295	19.5	89	5.9	1516	100.0
55-59	1175	73.3	333	20.8	95	5.9	1603	100.0
60-64	1138	72.8	345	22.1	81	5.2	1564	100.0
65-74	1855	70.5	651	24.7	127	4.8	2633	100.0
75 and over	1206	63.7	649	34.2	38	2.0	1893	100.0

Table 6. Size of Tumor

Tumor size (cm)	Patient No.	Patient %	Physician No.	Physician %	Mammography No.	Mammography %
0.1-1.0	723	9.6	259	11.0	108	26.2
1.1-2.0	2522	33.4	843	35.8	150	36.4
2.1-3.0	2076	27.5	655	27.8	69	16.7
3.1-5.0	1633	21.6	446	18.9	63	15.3
5.1+	590	7.8	151	6.4	22	5.3
TOTAL	7544	100.0	2354	100.0	412	100.0

SOURCE: Nemoto, et al., "Breast Cancer Detection in the US," Journal of Surgical Oncology, Vol. 21 (1982), pp. 180-185.

Table 7. Extent of Axillary Metastasis

Number of positive nodes	Patient		Physician		Mammography	
	No.	%	No.	%	No.	%
0	4409	58.3	1407	63.0	344	73.4
1-3	1718	22.7	448	20.0	68	14.9
4-5	435	5.8	108	4.8	20	4.4
6-9	434	5.7	114	5.1	9	2.0
10-15	335	4.4	103	4.6	11	2.4
16+	230	3.0	53	2.4	13	2.9
TOTAL	7561	100.0	2233	100.0	455	100.0

SOURCE: Nemoto, et al., "Breast Cancer Detection in the US," Journal of Surgical Oncology, Vol. 21 (1982), p. 185.

Table 8. Breast Cancers Detected During the Five-Year Breast Cancer Detection Demonstration Project Compared with the Four-Year Health Insurance Plan of Greater New York Screening Program

[illegible] Modality*	[illegible]				HIP***			
	Ages 40–49 at Surgery		Ages 50–59 at Surgery		Ages 40–49 at Surgery		Ages 50–59 at Surgery	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Mammography Only	270	35.4	540	42.1	6	19.4	27	41.5
Mammography & Physical Examination	381	50.0	638	49.7	6	19.4	12	18.5
Physical Examination Only	100	13.1	86	6.7	19	61.3	26	40.0
Unknown	11	1.4	19	1.5	0	0.0	0	0.0
Total	762[†]	100.0	1,283[††]	100.0	31	100.0	65	100.0

*Includes modalities that have findings with one or more features interpreted as suspicious of malignant or benign breast disease.

**BCDDP cancers shown in this table include only those cancers detected following a surgical recommendation made at an annual or exit/repeat screening.

***From Shapiro S. Evidence on screening for breast cancer from a randomized trial. *Cancer* 39 (suppl): 2772–2782, 1977.

†Includes 30 breast cancer cases in which a mammogram was not performed for any reason such as exam refused, exam not recommended for a woman under 50 years of age, or exam technically not satisfactory. Exclusion of these cases changes the distribution of suspicious modalities to: Mammography Only 36.9 percent, Mammography and Physical Exam 52.0 percent, Physical Exam Only 9.6 percent, and Unknown 1.5 percent.

††Includes 17 breast cancer cases in which a mammogram was not performed for any reason such as exam refused or exam technically not satisfactory. Exclusion of these cases changes the distribution of suspicious modalities to: Mammography Only 42.7 percent, Mammography and Physical Exam 50.4 percent, Physical Exam Only 5.5 percent, and Unknown 1.5 percent.

SOURCE: L. H. Baker, M.D., "Breast Cancer Detection Demonstration Project: Five-Year Summary Report," Cancer Journal for Clinicians, Vol. 32 (1982), p. 26.

Table 9. Breast Cancers Stratified by Lesion Size and Modality Findings*

Breast-Cancer Modality	Noninfiltrating Breast Cancers		Infiltrating Breast Cancers ≤1 cm		Infiltrating Breast Cancers ≥ 1 cm		Breast Cancer Size Not Specified**		Total Number of Breast Cancers Detected***	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Mammography Only	481	50.0	166	32.6	631	33.7	184	38.4	1 481	41.6
Mammography & Physical Examination	388	13.0	138	36.4	1 038	55.5	252	47.1	1 683	47.3
Physical Examination Only	43	3.5	33	8.4	181	9.6	73	13.7	308	8.7
Unknown	20	2.6	10	2.7	41	2.2	14	2.6	85	2.4
Total	782	100.0	371	100.0	1 871	100.0	533	100.0	3 557	100.0

* Only cases with lesion findings with one or more features interpreted as suspicious of malignant or benign breast disease.

** Breast cancer data not specified includes cancers for which the Hospital Pathology Report did not give the specific lesion size or for which a breast pathologist did not carry out a slide review.

*** Includes cancers detected following a surgical recommendation at an annual or early recall screening, or when a woman saw a surgeon prior to a scheduled early recall screening.

SOURCE L. H. Baker, M.D., "Breast Cancer Detection Demonstration Project: Five-Year Summary Report," Cancer Journal for Clinicians, Vol. 32 (1982), p. 27.

Table 10. Basic Information About the European Breast Cancer Screening Programmes

Programme	No screened, first cohort	Age and screening interval	Primary screening method	
			Mammography	Film interpretation
Florence (Italy) 1970 No controls	24,907 ? 57% of population	40–70 years. 24–30 m since 1975 longer before	Mediolateral and craniocaudal	Radiologist
Utrecht (Netherlands) 1974 Control national data	13,943. 71.5% of population	50–64 years. 12, 18, and 24 m	Mediolateral and craniocaudal xeroradiography	Two trained radiographic technicians
Nijmegen (Netherlands) 1974 Control local town Arnhem	ca. 24,370. 69% of population	35–65 years. 35+ years after 1977. 18 x 24 m	Mediolateral and craniocaudal only if technician suspects abnormality	Radiologist
Malmö (Kopparberg county, Sweden) 1977 Control randomised communities in the county	34,187 84% of population. 93% aged 40–70 years	40+ years. 18–30 m	Oblique	Radiologist
Malmö (Sweden) 1977 Control randomised individual females in same population	15,548 74% of population	45–69 years. 20–22 m	Oblique and craniocaudal	Radiologist
Turku (Finland) 1977 No controls	30,000. 84% of population	35–60 years. 60 m		Radiologist
Guildford (Surrey, UK) 1979 Control four defined similar districts	16,586. 69% of registrations ca. 75% of population	45–64 years. 18 x 24 m with clinical exam. in intermediate years	Oblique. craniocaudal may be requested if clinical abnormality found	Trained Dr who examines subject, 2nd opinion by radiologist
Edinburgh (Scotland, UK) 1979 Control = Guildford + a separate internal control group	> 12,000 ca. 80% of population	45–64 years as Guildford	Oblique and craniocaudal	Trained Dr with no access to clinical data. 2nd opinion by radiologist

Table 10. Basic Information About the European Breast Cancer Screening Programmes (cont'd.)

Clinical examination	Second stage screening	Referral system	Cancers detected
Two Drs a surgeon and a radiologist	Clinical examination Further mammographic views, thermographs galactography and needle aspiration cytology	Report to Family Dr	5/1,000
Radiographic technician		Report to Dr recommending referral for biopsy 18/1,000 or benign lesions found additional biopsies 4.5/1,000 screened Ca: benign 1:1.4 or 1:5	7.6/1,000 6.5/1,000 invasive
		Radiological report to Dr who decides referral policy Referred 14.4/1,000 40.5/1,000 biopsied Ca: benign 1:1	5.2/1,000 4.5/1,000 invasive
	Further mammographic views, magnification mammography, galactography, and needle aspiration cytology 36/1,000 screened	Direct referral for specialist assessment 18/1,000 screened 12/1,000 biopsied Ca: benign = 1:0.5	6.9/1,000 6.3/1,000 invasive
	As Falun 33/1,000 screened	Direct referral for specialist assessment. 17/1,000 screened 12/1,000 biopsied Ca: benign = 1:0.7	5.1/1,000 6.3/1,000 invasive
Trained nurses	Oblique-view mammography in 23% of females (problematic females 35–55 and all over 60 years)		1.6/1,000
Trained Dr	As Falun + specialist assessment, clinical examination Ultrasound and further assessment 88/1,000 screened	Direct referral to project surgeon. 30/1,000 screened 15/1,000 biopsied. Ca: benign = 1:1.8	5.5/1,000 4.7/1,000
Trained nurses	None but second clinical opinion available at screening visit if required	Referral via Dr or direct to specialist. ca. 30/1,000 screened 10/1,000 biopsied. Ca: benign = 1:2	5.9/1,000 4.8/1,000 invasive

SOURCE: Gad, et al., "Screening for Breast Cancer in Europe: Achievements, Problems, and Future," Recent Results in Cancer Research, Vol. 90 (1984), pp. 182-183.

Table 11. Estimate of the Expectancy Gains and Losses From Screening*

Number of Years of life expectancy per 1,000 women screened					
Age at Entry (Years)	Gain from annual screening		Loss per mammographic examination according to dose (rad)		
	First	Second	0.1	0.4	0.8
35-39	6.3	2.8	0.09	0.36	0.7
40-44	15.3	7.5	0.06	0.24	0.48
45-49	27.7	11.4	0.04	0.16	0.32
50-54	21.3	1.7	0.03	0.12	0.24
55-59	15.7	4.8	0.02	0.08	0.16

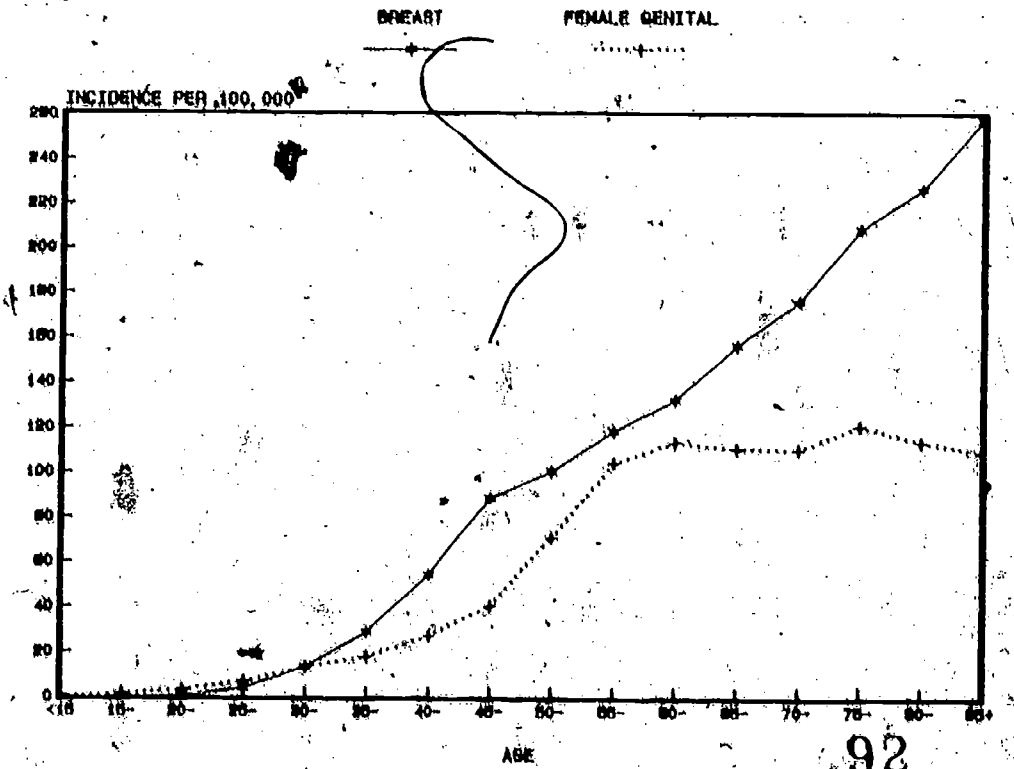
* Table modified from Siedman 1977 to assume risk factor of 3.3 excess cancers/million women/year/rad at the doses given.

SOURCE: S. A. Feig, "Benefits and Risks of Mammography," Recent Results in Cancer Research, (1984), p. 22.

FIGURE 1

AGE-SPECIFIC INCIDENCE RATES

ALL SEER AREAS (EXCLUDING PUERTO RICO), 1973-77

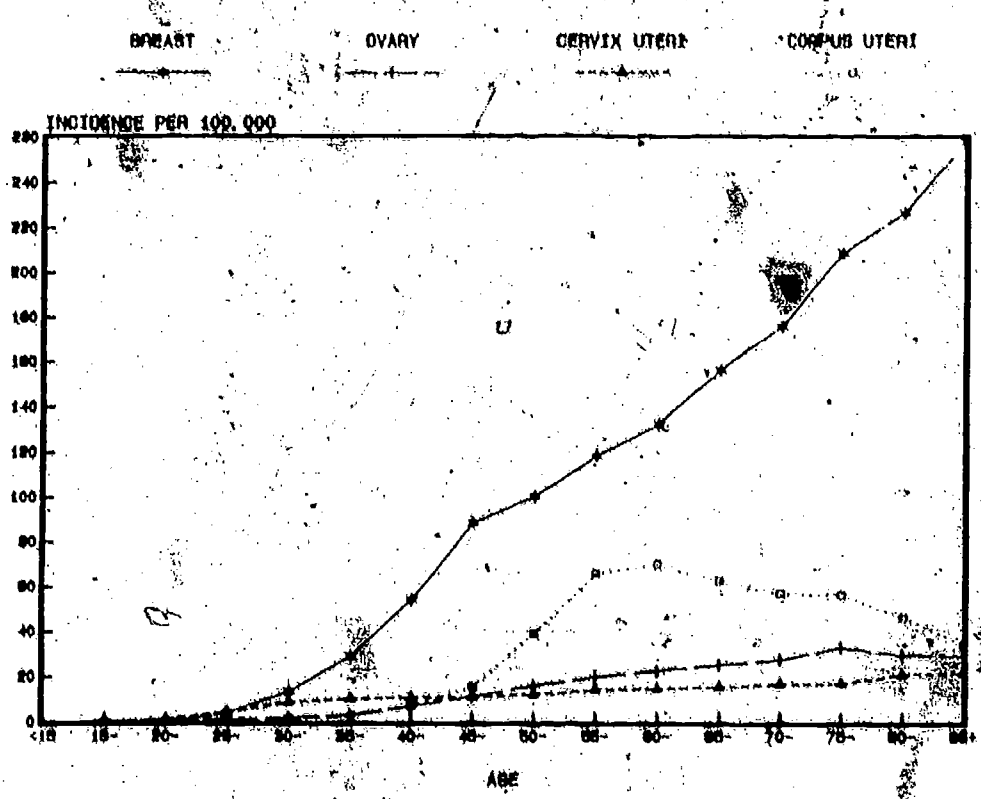


MICHIGAN CANCER FOUNDATION-DIVISION OF EPIDEMIOLOGY 6/21/84

FIGURE 2

AGE-SPECIFIC INCIDENCE RATES

ALL SEER AREAS (EXCLUDING PUERTO RICO), 1978-77

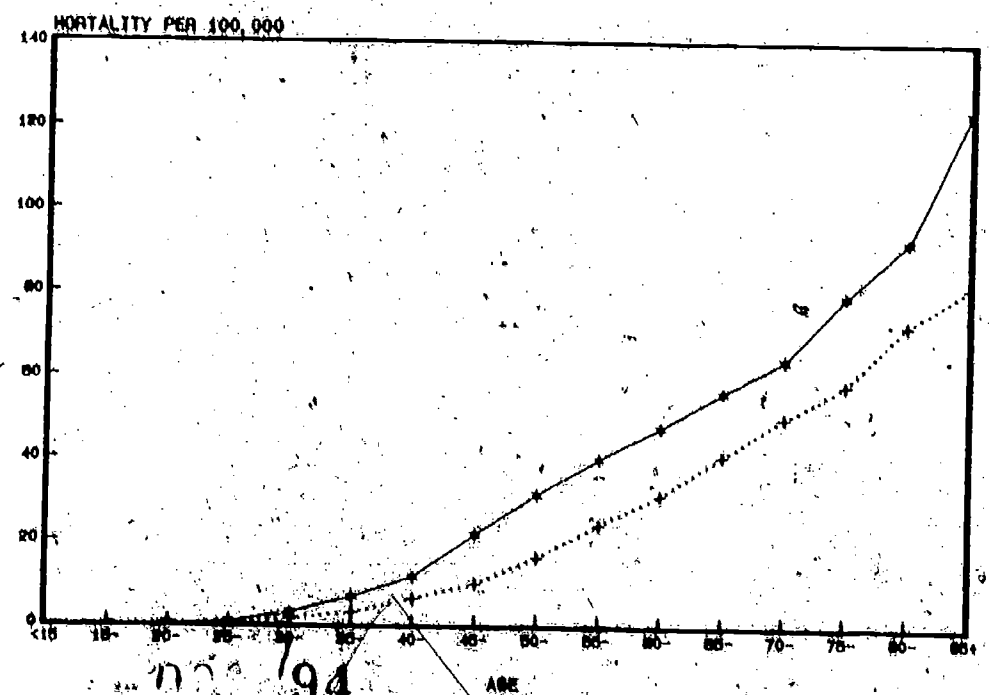


MICHIGAN CANCER FOUNDATION-DIVISION OF EPIDEMIOLOGY 8/21/84

FIGURE 1

AGE-SPECIFIC MORTALITY RATES

ALL SEER AREAS (EXCLUDING PUERTO RICO), 1979-77



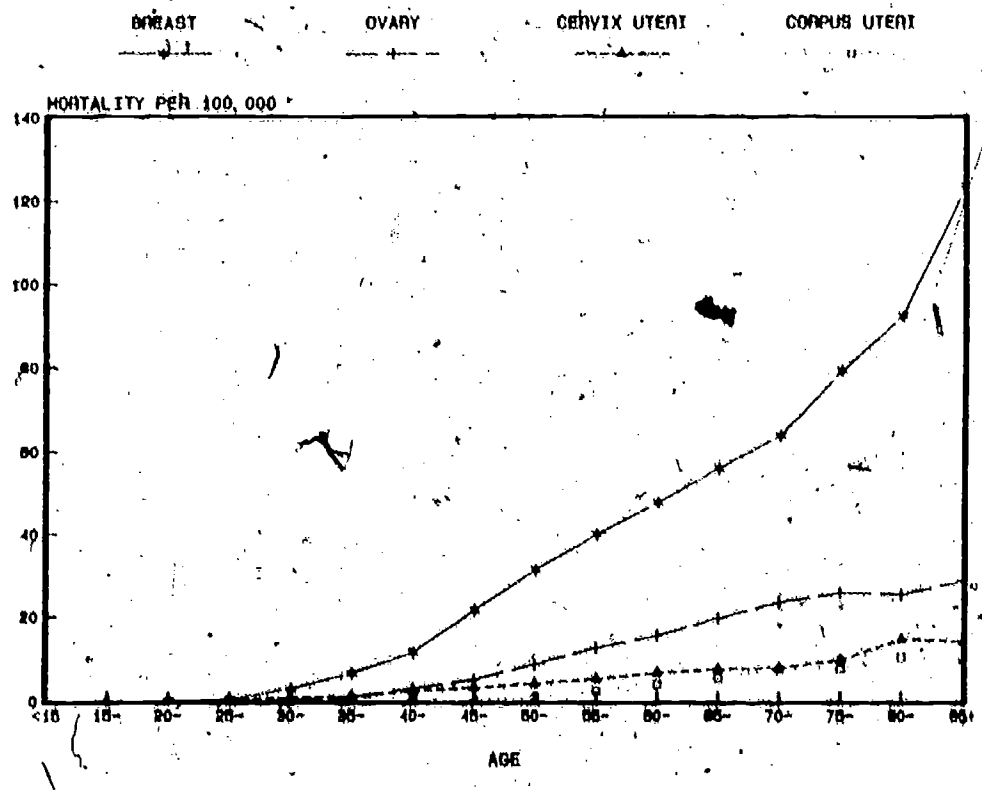
94

MICHIGAN CANCER FOUNDATION-DIVISION OF EPIDEMIOLOGY 8/21/84

FIGURE 4

AGE-SPECIFIC MORTALITY RATES

ALL SEER AREAS (EXCLUDING PUERTO RICO), 1973-77



MICHIGAN CANCER FOUNDATION-DIVISION OF EPIDEMIOLOGY 8/21/84

Ms. OAKAR. Thank you very much, Doctor.
Dr. Hubay?

STATEMENT OF CHARLES HUBAY, M.D.

Dr. HUBAY. It's an honor and privilege to be here today. I do want to bring some encouraging facts about therapy of breast cancer this morning. We have heard mainly doom and gloom this morning, and as you will notice, all the women at this table this morning that were testifying are alive and apparently well, some 8 to 10 years following their surgical procedures, and I think that speaks something for the medical profession, that we have at least been able to help a number of women achieve long-term survival, without evidence of disease.

One of the things that I do not want to get into today is the merits of one procedure over another, except to reemphasize what Dr. Crile has told us this morning, that we are no longer finding it necessary to do the old-fashioned, radical, operation, except in very unusual circumstances, where the tumor is so large it's grown into the muscles, so we have to take off the muscles of the chest wall.

Modified, radical mastectomy remains the gold standard of treatment for breast cancer in this country today. However, with earlier diagnosis, perhaps some of the lesser procedures that we are doing and I do them, partial mastectomies, things of this sort, for very early carcinoma in situ have a role.

The incidence of breast cancer, as we have heard this morning over and over again, does affect a large number of American women. And it is one of the two leading causes of death from cancer, the other being carcinoma of the lung, secondary to cigarette smoking.

Now, untreated breast cancer is fatal. About 80 percent of women with untreated breast cancer will die within 5 years. The vast majority of them are dead and gone at the end of about 3 years. We do know, however, that early treatment and detection of breast cancer is very effective. We have data from our own studies of a cooperative study, funded by NCI, which show that if we can get the tumor early, before it spreads anywhere, that over 90 percent of our women are alive at the end of 5 years. And I've documented that as appendix A in my testimony.

One can see, by scanning the data, that of patients who have a hormone receptive or responsive tumor, and have a modified radical mastectomy, over 90 percent of them are alive at the end of 5 years. It's not perfect but it's a far cry from the untreated patient in which only 20 percent are alive with cancer at the end of 5 years.

Ms. OAKAR. You can test that hormone receptor because for the benefit of lay people like myself——

Dr. HUBAY. I will be coming to that in a moment.

Ms. OAKAR. OK; I'm sorry.

Dr. HUBAY. I just wanted to point out that in over 500 women that we've done modified radical mastectomies on, over 90 percent of the women who have a hormone receptive tumor are alive at the end of 7 years, which is a far cry from the previous data that's available in any other form of treatment.

Well, unfortunately, a large number of women get to us too late. They may have very tiny tumors and they have already spread throughout the body, as Dr. Threatt just pointed out.

Not all women, however, have systemic disease at the time the diagnosis is made. I would think that if that were the case, our data showing 90 percent alive, 90 percent survival at 7 years for earlier breast cancer would belie some of the ideas that have been presented here today.

Now, unfortunately there are a number of women, and we have a number of black women in the city of Cleveland that are on our study, some of the black women that we see in our clinics and our practice at our hospital have a worse prognosis; also in appendix B, as noted here, one can see that the women who have estrogen receptors, do better than women who do not have these hormone receptors in their breast cancers. The exact reason for this is unknown. Perhaps they are more aggressive tumors from the very beginning and, therefore, tend to spread throughout the body. The survival and recurrence rates are not as favorable as they would be in a number of other women.

Lymph node involvement remains the most important factor in the prognosis of breast cancer. Women who have no nodes involved, that is, the tumor has not spread from the breast to the axilla, are best survivors. Of women whose nodes are completely removed and analyzed, if one to three nodes are involved with breast cancer, their survival rate is better, far better, than women who have four or more nodes involved. We, have shown that if women have more than four nodes involved, about 80 percent of these women will have a recurrence by the end of 5 years.

So, I think this points out again that the earlier we can make the diagnosis and institute some sort of effective therapy, we have a much better prognosis in these particular patients.

For about 10 years, thanks to some of the pioneering work by Dr. Jensen and Dr. Maguire, we have been able to ascertain the hormone receptiveness of certain breast cancers. We find that if we evaluate our breast cancer patients, about 76 percent of the women that have breast cancer will have estrogen receptors and progesterone receptors in the tumors. We know by following these patients and treating them with various forms of hormone or antihormone therapy that this group of women do much better than the women who do not have estrogen receptors in their breast cancers.

The hormone receptors, give us another club as to therapy and will be helpful in the long-term solution and treatment of the breast cancer problem.

Ms. OAKAR. Do you treat that, then, Doctor, for those women who have this positive receptor, do you treat that, then, with medication, or how do you treat it?

Dr. HUBAY. Yes. We have—fortunately, on the horizon are some antiestrogen drugs. I don't know whether I should mention the trade names of these drugs before this hearing, but Tomoxifen is a commonly used term for one of the antiestrogen drugs. And in our studies we have shown that treating women with estrogen receptor positive tumors, with the antiestrogen drug tomoxifen, that the long-term survival and disease-free survival are improved both in the postmenopausal and the premenopausal group.

Ms. OAKAR. After the woman has surgery, should they be taking this if they have that receptor, should they be taking this kind of drug?

Dr. HUBAY. We think that they should, particularly if they have positive lymph nodes. If the lymph nodes are free of tumor, we don't know the answer to that, Ms. Oakar.

Ms. OAKAR. I see.

Dr. HUBAY. But we are instituting studies now and studies are underway in our own laboratories.

Ms. OAKAR. There is an FDA controversy about whether you allow that drug to be used for women with breast cancer and don't have the, perhaps——

Dr. HUBAY. The FDA today, I think, has limited its use in widespread breast cancer.

Ms. OAKAR. Yes.

Dr. HUBAY. I think emerging data will force them to change their mind and make it available to us for treatment for lesser involved patients.

Ms. OAKAR. Right.

Dr. HUBAY. Since modern day therapy is effective if carried out early for breast cancer, the greatest needs, as I see it, are diagnostic methods to complement the physical examination. Mammography, if more widely available, would detect cancer earlier and save lives.

The nuclear magnetic resonance examination; the NMR's that we're hearing a lot about today, are being used on an experimental basis at our own hospital. It is now emerging as a better method, perhaps, to detect tumors, but at the present time is not widely available. It is used in our own institution to help clarify tumors that are problems in certain patients.

We continue to stress that early detection and treatment of breast cancer results in long-term disease-free survival. Our goal should be to make available to all women in this country an economical and effective diagnostic method to allow early therapy for the cure of this devastating affliction. And I appreciate the opportunity for presenting some of our research data before this committee.

[The prepared statement of Dr. Hubay follows:]

PREPARED STATEMENT OF CHARLES A. HUBAY, M.D., PROFESSOR OF SURGERY, CASE WESTERN RESERVE UNIVERSITY, SCHOOL OF MEDICINE, CLEVELAND, OH

The incidence of breast cancer has been increasing and now is estimated to develop in 1 of 11 American women. It is also one of the two leading causes of death from cancer.

Untreated cancer of the breast is fatal in 80% of women within five years. Early detection and treatment is effective, however, resulting in over 90% survival at five years. (Appendix A) Our data has shown that certain black women with breast cancer have a worse prognosis for long-term survival. (Appendix B)

Unfortunately, a large number of women with breast cancer will have spread of tumor to lymph glands in the axilla by the time the diagnosis is established. Lymph node involvement remains the dominant factor in prognosis for long-term disease free survival. Observations of patients with lymph node involvement have shown that breast cancer patients with 1-3 nodes involved with tumor have a better long-term prognosis than patients with 4 or more involved nodes. (Appendix C)

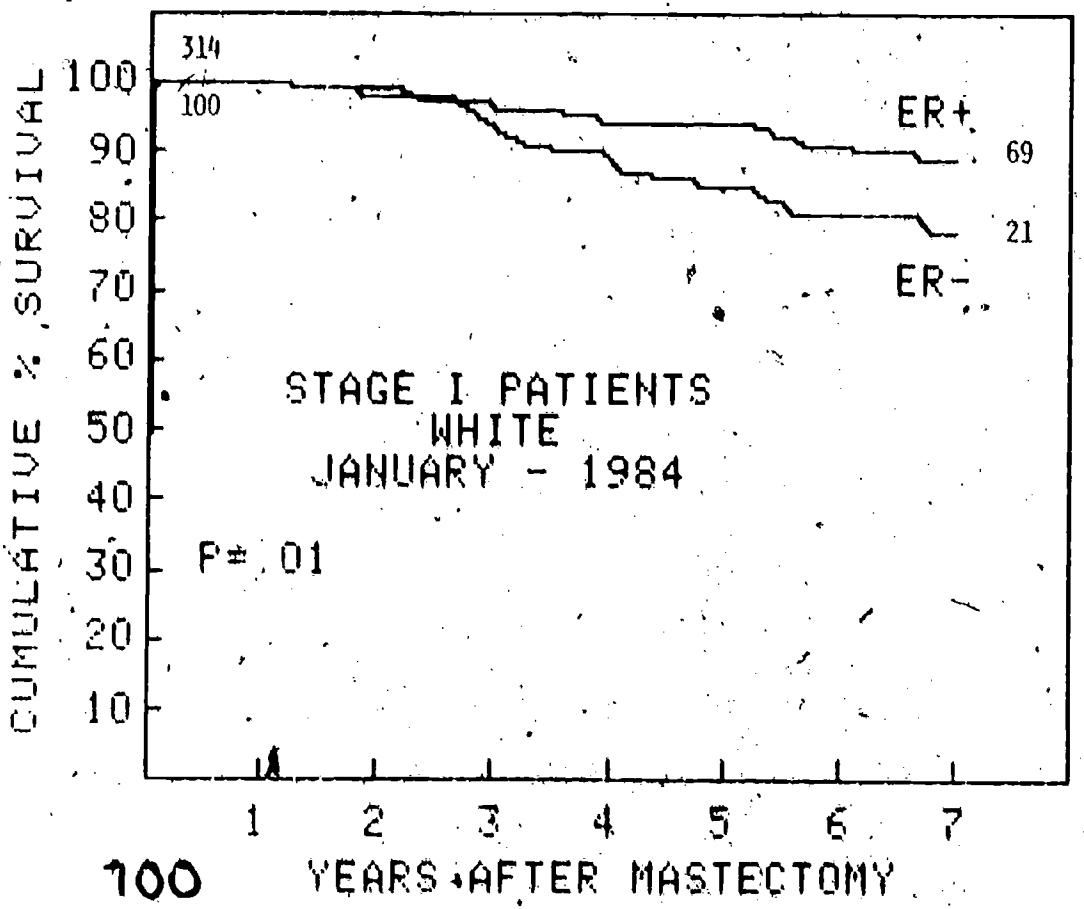
Studies over the past decade have demonstrated the presence of hormone receptors in human breast cancer cells. Hubay and colleagues in their long-term clinical trial on women with Stage I (no positive nodes) and State II (positive nodes) opera-

ble breast cancer have shown that women with breast cancer containing hormone receptors (estrogen and progesterone) have a significantly longer disease free survival (Appendix D) and overall *total* survival. (Appendix E) They have also shown that the anti-estrogen drug Tamoxifen (Nolvadex) is a useful drug in both pre- and postmenopausal breast cancer patients with estrogen receptor positive tumors.

Since modern day therapy is effective if carried out early for breast cancer, the greatest needs are diagnostic methods to complement physical examinations. Mammography, if more widely available would detect cancer earlier and save lives. NMR (Nuclear Magnetic Resonance) examination is now emerging as a method to help clarify tumors in problem patients.

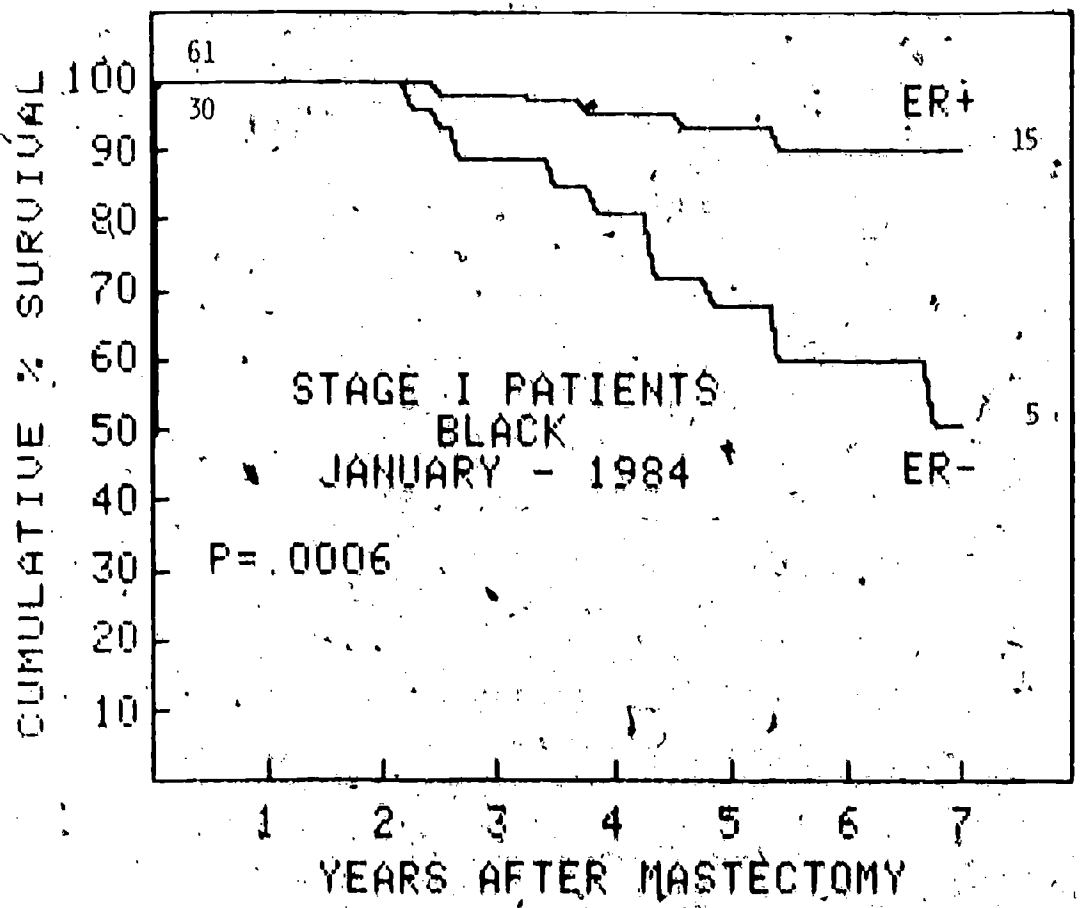
We continue to stress that early detection and treatment of breast cancer results in long-term disease free survival. Our goals should be to make available to all women economical and effective diagnostic methods allowing early therapy for the cure of this devastating affliction.

[See appendix 2, p. 182 for additional material submitted for the record by Dr. Hubay.]

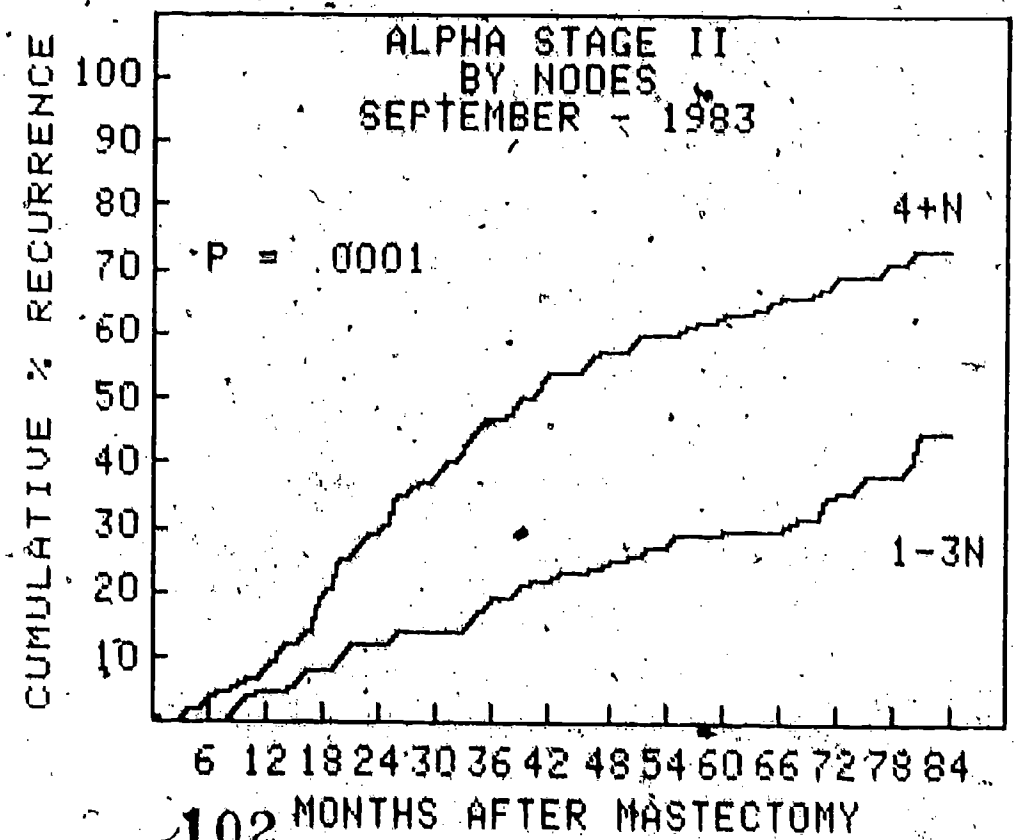


100

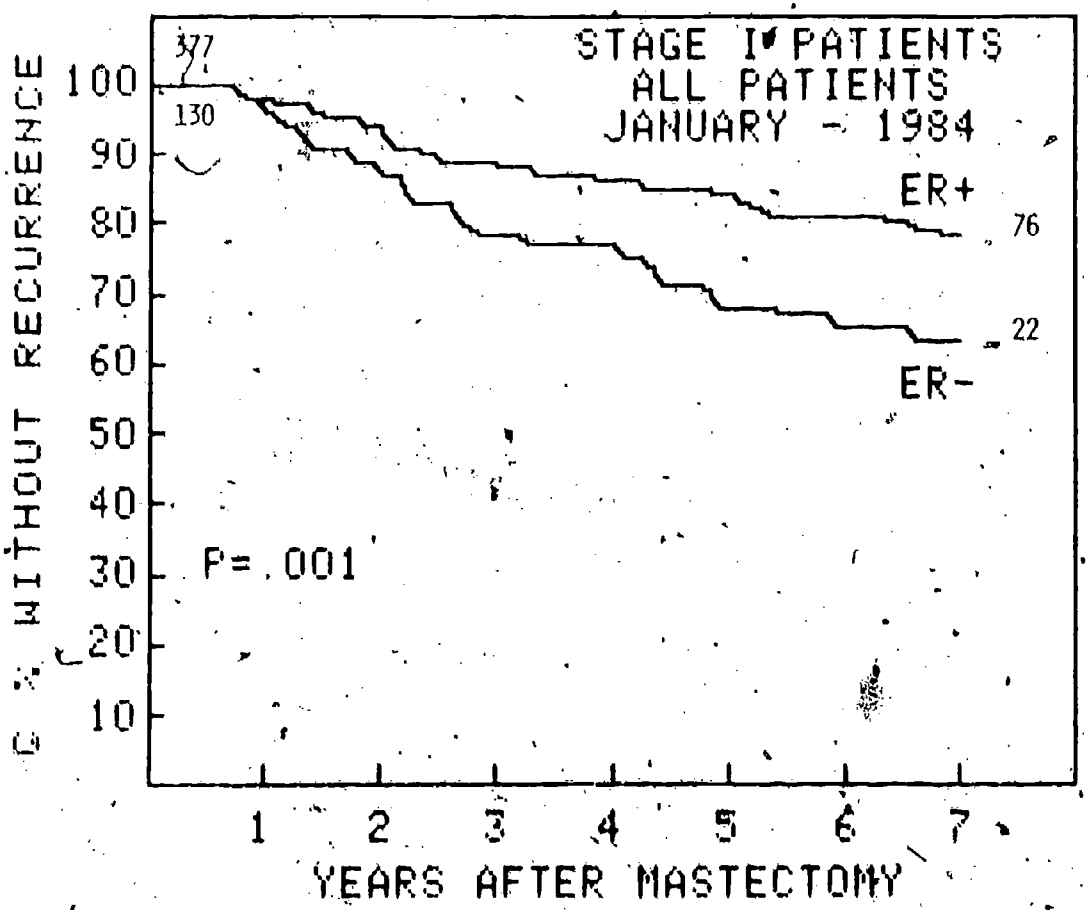
APPENDIX A


61
30
ER+
15
5
ER-
STAGE I PATIENTS
BLACK
JANUARY - 1984
P=.0006
CUMULATIVE % SURVIVAL
100
90
80
70
60
50
40
30
20
10
1
2
3
4
5
6
7
YEARS AFTER MASTECTOMY

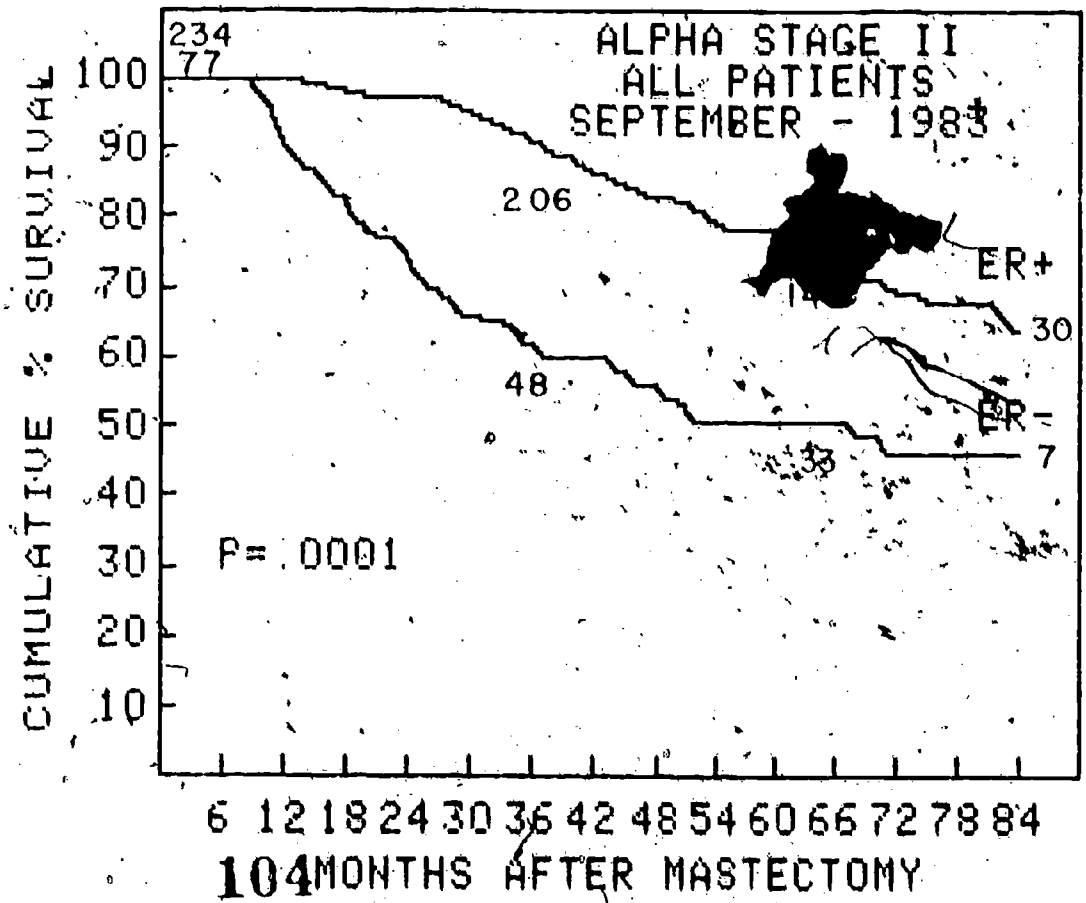
APPENDIX.B


ALPHA STAGE II
BY NODES
SEPTEMBER - 1983
P = .0001
4+N
1-3N
CUMULATIVE % RECURRENCE
100
90
80
70
60
50
40
30
20
10
6 12 18 24 30 36 42 48 54 60 66 72 78 84
MONTHS AFTER MASTECTOMY

APPENDIX C


STAGE I PATIENTS
ALL PATIENTS
JANUARY - 1984
377
130
ER+
76
22
ER-
P=.001
% WITHOUT RECURRENCE
100
90
80
70
60
50
40
30
20
10
1
2
3
4
5
6
7
YEARS AFTER MASTECTOMY

APPENDIX D


234
77
ALPHA STAGE II
ALL PATIENTS
SEPTEMBER - 1983
206
ER+
30
48
ER-
7
33
P=.0001
CUMULATIVE % SURVIVAL
100
90
80
70
60
50
40
30
20
10
6 12 18 24 30 36 42 48 54 60 66 72 78 84
104 MONTHS AFTER MASTECTOMY

APPENDIX E

Ms. OAKAR. Well, we think it's important and we're delighted to have you here, Doctor.

Unfortunately, the questions I have will have to be quick ones because we have another panel and they're outstanding as well.

Dr. Wynder, you talked about dietary fat and you're sure, I think you said, that there is a real connection between diet and the prevention of cancer. Let me ask you a question. Why don't doctors, after a woman knows she has cancer, and let's say she has the surgery or whatever it is she's supposed to have to be cured, why don't doctors tell her something about diet? You were talking about prevention. But let's deal with the cancer patient. Why don't doctors do that and give an individual a diet, let's say, to follow, or some guidelines? It's almost as if they leave them high and dry after—not all doctors, but I mean some of the problems that women seem to communicate is, "I just don't have any kind of advice as to what I should do or not do"?

Dr. WYNDER. As you know, most doctors haven't been particularly well trained in nutrition in medical school. That may be one reason.

Ms. OAKAR. You mean medical schools should emphasize the knowledge of diet?

Dr. WYNDER. Yes. I think with trials now being conducted by the National Cancer Institute on the low fat diet on postmenopausal stage II breast cancer patients, some early results could be forthcoming within 2 years of the trial. Then if the trial is positive, the National Cancer Institute, no doubt, would provide better information to doctors. In the meantime, statements made by Dr. DeVita from the National Cancer Institute and by the American Cancer Society, should be distributed to physicians. Certainly, if I were treating breast cancer, there is no reason why I cannot apply a low-fat diet even today, because one thing is sure about a low-fat diet, it doesn't do any harm. In addition to possibly affecting your breast cancer there are a variety of other diseases that would benefit from a low-fat diet.

Ms. OAKAR. Can you give us a quick idea about what you're saying when you talk about a low-fat diet.

Dr. WYNDER. Right now Americans consume about 40 percent of their calories from dietary fat. I'd like to see this reduced to 25 percent of total calories.

The dairy industry should provide us with low-fat milk, meat industry with more low-fat meats, and housewives and mothers who are responsible not only for what they eat but for what the entire family eats, should become more aware of where most of our dietary fats come from.

In the adult population some 40 percent comes from meat sources, some 20 percent comes from dairy sources, and the other 40 percent are hidden sources coming in part from the way we prepare fish and meat. In children it's quite reversed. Some 45 percent comes from dairy sources.

It is particularly important to provide our children with the appropriate dietary intake very early in life, and particularly we should start children in low-fat content of dairy products.

Ms. OAKAR. Dr. Crile, you mentioned a number of things and, of course, how important is it to women in terms of the psychology

behind how a woman would be affected psychologically by, let's say, having a radical mastectomy? We had one person who obviously was deeply affected and the family by the manner in which she was treated in terms of a radical mastectomy that she believes was not necessary.

Does that involve—is that in any way involved in the curing of the cancer, the stress and psychological impact that takes place when you——

Dr. CRILE. I don't think so.

Ms. OAKAR. You don't think so?

Dr. CRILE. I don't think it's related to the cure at all.

Ms. OAKAR. Then why not be more sure by having your entire breast removed rather than the lump removed? I guess if it's not related to the cure, what's the benefit of just taking out the lump when that's the only necessity?

Dr. CRILE. She feels intact.

Ms. OAKAR. She feels better about herself?

Dr. CRILE. She feels intact.

Ms. OAKAR. I guess that's what I was trying to infer.

Dr. CRILE. Yes.

Ms. OAKAR. When I mentioned cure.

You mentioned the immediate reconstruction for those women who do have to, let's say, have a mastectomy.

Dr. CRILE. Right.

Ms. OAKAR. Are you talking about immediately?

Dr. CRILE. That's about 30 percent. We're handling now about 30 percent as a partial mastectomy without radiation, about 30 percent of the lumpectomy with radiation and about 30 percent as modified radical.

Ms. OAKAR. But let's say a person had to have a modified radical. Do you then reconstruct the breast right——

Dr. CRILE. Right then.

Ms. OAKAR. Right then and there?

Dr. CRILE. Most of them.

Ms. OAKAR. Most of them?

Dr. CRILE. Yes.

Ms. OAKAR. What about if the patient has had radiation?

Dr. CRILE. Well, you see——

Ms. OAKAR. And then you had to have your breast removed?

Dr. CRILE. There aren't very many of those who have preoperative radiation without that being part of the designed program. We are not doing very many mastectomies after radiation. Radiation is a problem, always, with reconstruction. But all sorts of complicated reconstructions can be done, sliding in flaps of unradiated skin from elsewhere. That's a more complicated problem and a rare one.

Ms. OAKAR. Right.

Dr. Threatt, you and Rose Kushner mentioned the problems—a lot of women, for example, are afraid to get a mammography because they heard years ago that there was too much radiation involved. And yet we think—I think all the doctors are saying early detection is important.

And you were stressing equipment in training, and Rose did too. And she mentioned, I believe, that my own State of Ohio does not mandate that there's licensing involved with radiation.

What should we be doing, as legislators? Should we be legislating that or should we just insist that they be trained better? Or how do we detect—how does a hospital know if the equipment is—is there some type of equipment that is better than others? Can you just get into that briefly for a few seconds?

Dr. THREATT. There are two ways to do mammography, and they require quite different kinds of equipment. To do film mammography you must use a machine that does only mammography. It's designed for that. For xerography, regular x-ray equipment is used.

There is essentially no monitoring of radiation levels. I guess the States are responsible for that. I have been in practice at the University of Michigan for 14 years. I've never seen anybody come in to check the radiation levels.

Ms. OAKAR. So, you think that the States should be checking the radiation levels periodically?

Dr. THREATT. Yes. They should be doing it in a more active way than they are.

Ms. OAKAR. Right.

Dr. THREATT. I think in the large hospitals, the large clinics, there probably is no problem. The radiologists are very aware of the situation, not just for mammography but for all procedures.

But in the smaller hospitals and clinics this may be a different situation. So, I would think that the responsibility should lie with the States.

Ms. OAKAR. Right. But that it's important and that it's not quite being done now?

Dr. THREATT. It's very important that it be done, and really I don't know how well done it is.

Ms. OAKAR. I see.

Dr. Hubay, I know you've been doing really wonderful research in various areas and I know that's in your paper, and we do have another vote, unfortunately, but I'm going to ask you this question and maybe you can respond to it briefly. What is so magical about saying that a person or implying that a person—why do we choose five years as the magic number? Shouldn't it be 10 years, you know, after surgery?

Some of the patients, by the way, just had surgery. Not everybody has had—that appeared this morning had had their surgery for 8 or 10 years. Some just had it 2 years ago. Why do they choose five years?

Dr. HUBAY. I think that this goes back to the whole era where the radical operation was done, and I think that the initial data was so promising at the end of 5 years that was sort of the standard for other results.

Ms. OAKAR. Should we raise the standard to 10 years?

Dr. HUBAY. There are many of us that feel that breast cancer, perhaps, is never cured until the woman dies of something else at age 99. Then I would say she's cured. I prefer to call it long-term disease-free survival, at the present time.

Since we are seeking the facts and information, I would like to reemphasize today that when we're talking about partial mastectomy or lumpectomy, I think all the women here and elsewhere should realize that in 35 to 40 percent of instances, if one does a simple removal of the breast cancer in one area, breast cancer will

be left behind in foci in about 35 or 40 percent of women. This has been will established by Dr. Rosen, a pathologist at Memorial Hospital.

Now, that doesn't mean that the tumors cannot be treated. But I want them to realize that they are taking a chance on leaving tumor behind. There's no scientific argument about multicentric, residual carcinoma.

Ms. OAKAR. Dr. Crile, did you ever respond to that?

Dr. CRILE. I agree. I'm sure that we have that much multicentric cancer. The sad thing and the disturbing thing to me is that both Dr. Hubay and I have the same situation in our prostates right now, because about 50 percent of the people of our age have the same type of cancer in their prostates. And we're not rushing in to get a prostatectomy.

Ms. OAKAR. I see. Well, what if a person has carcinoma in situ? Should that person have her breasts removed or should we say that that can be arrested. What should we do about that situation?

Dr. CRILE. This is a very well localized, very early lesion. If there's no invasion, I think simple excision is sufficient in a large number of women.

Ms. OAKAR. I want to thank this panel very much, and we probably will have some other questions for the record, in writing, to you. I hope no one leaves because we have a final panel that is just outstanding, three more witnesses, and they're absolutely incredibly outstanding. So, I'm going to go vote and I will be back in 5 minutes.

[Brief recess.]

Ms. OAKAR. Our next panel is a very distinguished panel as well; Dr. Alfred Knudson, a senior member of the Fox-Chase Cancer Center, Institute for Cancer Research, in Philadelphia; Dr. Philip Strax, the director of the Guttman Breast Cancer Detection Clinic of New York, and Dr. William Feller, here in Washington, DC, who is the director of Georgetown University breast cancer followup study project, among other things.

Gentlemen, we're equally delighted to have you here and we're very grateful because we know you're very busy people. As are the other individuals who testified.

Dr. Knudson, would you like to begin?

PANEL THREE: CONSISTING OF ALFRED KNUDSON, M.D., PhD., SENIOR MEMBER, FOX-CHASE CANCER CENTER, INSTITUTE FOR CANCER RESEARCH, PHILADELPHIA, PA; PHILIP STRAX, M.D., DIRECTOR, GUTTMAN BREAST CANCER DETECTION CLINIC, NEW YORK, NY; AND WILLIAM FELLER, M.D., DIRECTOR, GEORGETOWN UNIVERSITY BREAST CANCER FOLLOWUP STUDY PROJECT, WASHINGTON, DC

STATEMENT OF DR. ALFRED KNUDSON

Dr. KNUDSON. Thank you, Ms. Oakar. I too wish to thank the subcommittee for the opportunity to speak on the subject of cancer, I have submitted a paper, which I do not intend to read.

It can't bear too much emphasis that environmental factors are important in many cancers, and particularly in breast cancer, where the oriental migration studies have shown quite clearly that

something in the environment must be invoked to explain cancer differences between Japan and the United States. Now we implicate smoking and diet as the two major environmental factors for many cancers.

There have been great frustrations about cure rates for cancer. The mortality of most cancers has not changed much, as you know, in 30 years, except for lung cancer increasing markedly and stomach cancer decreasing markedly. There have been some spectacular improvements in cure rates for some cancers, but, unfortunately, these are mostly for rare cancers, notably those in children, Hodgkin's disease, testicular cancer, and so on.

Ms. OAKAR. Doctor, is it because, for example, with respect to leukemia, you know, we had that hospital of Danny Thomas and others. Is it because, as Rose was trying to point out, I think, earlier, that we have really zeroed in on leukemia; studies that and determined we were going to do something about some diseases and not so much on breast cancer? I mean, does that play a role in it?

Dr. KNUDSON. I personally do not think so. I think there is a difference in the biology of these tumors.

Ms. OAKAR. I see.

Dr. KNUDSON. When I was a medical student, no child had ever been cured of leukemia. And the cure rate is now 60 percent. You remember that leukemia in a child is generalized through the body when it's diagnosed. Yet, we cannot cure any of the common adult cancers with chemicals when they have spread through the body. So, many of us feel that there needs to be some whole new approach to the treatment of generalized cancer of the more common types.

I'd like to say just a few words, then, about where we are in understanding cancer. It's now generally regarded as a genetic disease of our body's cells. That is, in most if not all cases, the genetic constitution of the cancer cells in a person is different from the genetic constitution of the other cells in the body.

Two questions are very important. One is, what causes this change? And the other is, what is the change? The first would have importance for prevention and the second for treatment.

If mutations are very important, we must remember that mutations occur spontaneously. They are important for evolution. They occur at some spontaneous background rate and this leads us to think that we will always have cancer, because it will occur spontaneously to some extent. My own estimate is that about 15 percent of cancer in the United States is owing to spontaneous changes.

Some individuals are born with a genetic change in all the cells of their body that increases their risk for spontaneous cancer. We call this hereditary predisposition to cancer. A very strong predisposition, I think, accounts for perhaps 5 percent of the cancer in this country. For example, there are at least three different hereditary forms of breast cancer, and somewhere around 5 to 10 percent would be the total for hereditary forms of breast cancer.

Now, we know that the genetic constitution of cells can be changed by hereditary agents, radiation, chemicals, and viruses. But when we say 80 percent of cancer is environmentally induced, we must remember that the people that get cancer as a result of this exposure may not be random individuals. They may be geneti-

cally predisposed to environmental carcinogenesis. This is a subject under intensive investigation at the present time. We would like very much to know whether there are, for example, certain people who should not smoke—well, many of us think no one should smoke but it may turn out that some smokers are much more likely to get cancer than others.

As far as understanding what's wrong in cancer, there is a lot of excitement at the present time. Many people in cancer research feel that the work of the last 3 or 4 years in cancer is coming to a head and that in the very near future we will understand how some cancers originate, and what is wrong in them.

I can't promise you that that will lead to new ways of dealing with cancer. But we think that it can't hurt.

The breakthrough came as a result of, really, the large virus program of the National Cancer Institute, and the subsequent discovery that some——

Ms. OAKAR. Was that financed through Federal funds?

Dr. KNUDSON. Yes.

Ms. OAKAR. Without those funds we might not have had it?

Dr. FELLER. Accelerated funding.

Ms. OAKAR. Right.

Dr. KNUDSON. It had a great impact because it taught us about two classes of viruses, among other things, one of which causes cancer because it has a special gene called an oncogene, that turns almost every cell that the virus hits into a tumor cell. There is another class that causes cancer at a very low rate and does not have any oncogene. It was discovered that when this kind of virus does cause cancer, it does so by sitting down next to an oncogene that the host has. We are the ones who have the oncogenes; some viruses have carried them away and cause cancer easily, while others must find one of our oncogenes.

Of course, these oncogenes aren't there to make cancer in us, and one of the objects of research in this field is to find out what is the normal function of oncogenes. But when they work abnormally, they seem to cause cancer.

We do not need to have viruses to turn on these oncogenes. They can be made abnormal by radiation, chemicals and other means.

I have been interested in another class of cancer gene, which I call anti-oncogene, and which is associated with hereditary cancers. The study of two children's cancer, retinoblastoma and Wilms' tumor, has been particularly fruitful in this respect, and has taught us that this is a different class of gene from the oncogene.

Some children with retinoblastoma have a hereditary form and some have non-hereditary, and I remind you that the same situation applies to breast cancer. We have discovered in retinoblastoma that the hereditary and non-hereditary form both begin with the same genetic abnormality, and we think that may be the case for breast cancer. So, the study of hereditary breast cancer could not only help us in identifying persons at risk, but it might also tell us about the basic defect in the non-hereditary form, because it has done that in these two children's cancers.

I'd also make a plea that we, in cancer research, not dedicate too much attention to just one kind of cancer, because we often learn from one about another. I'd also like to point out that oncogenes

have now been found in yeast cells, in fruit flies, and in other organisms, and the study of them there may be very helpful.

I conclude by saying that some amount of cancer seems to result from spontaneous biological processes that are not avoidable, and we'll have to live with it, so we should continue to be interested not only in prevention but also in treatment.

Second, major changes in cancer incidence require new preventive measures. I don't need to elaborate on that. Finally, major changes in cure rates require some new therapeutic approaches, and they current research on cancer mechanisms is the best bet for finding such new measures at the present time.

[The prepared statement of Dr. Knudson follows:]

PREPARED STATEMENT OF ALFRED G. KNUDSON, JR., M.D., PH.D., SENIOR MEMBER, INSTITUTE FOR CANCER RESEARCH, FOX CHASE CANCER CENTER, PHILADELPHIA, PA

Cancer is the second killer in industrialized nations. There are numerous kinds of cancer and their incidences vary considerably world-wide. For example, the four major cancer killers in the USA and China show no overlap. Studies of migrants and of variations within nations by year, geography, occupation, and personal habits all suggest that much of cancer is environmentally induced.

The incidences of most cancers increase greatly with age. This feature has been related to experimental work indicating that cancer generally arises in two or more steps; i.e., some cell of the body must undergo 2 or more changes to be transformed into a cancer cell, which then multiplies in an uncontrolled manner. The older a person is, the more likely he or she is to harbor cells that have accumulated one of these steps.

In the USA over the past 30 years or so there have been few truly major changes in the incidences and cure rates for most cancers. The most extreme changes have been a great increase in lung cancer and a striking decrease in stomach cancer. Smoking accounts for the former, whereas changes in food handling and/or diet may account for the latter.

Spectacular improvements in cure rates have been accomplished for some rare cancers, e.g., acute leukemia and several other cancers in children, Hodgkin's disease, testicular cancer, and choriocarcinoma. Even very early diagnosis has helped surprisingly little for most of the common cancers, causing many investigators to concentrate their attention on the biology of cancer in the hope of generating new ideas for treatment.

Cancer is now generally regarded as a genetic disease of somatic cells, i.e., in most, if not all, cases the genetic constitution of cancer cells is different from that of the other cells of the body.

Two questions seem important:

1. What causes this change?
2. What is the change?

Causes:

1. Mutations occur spontaneously at some background rate, so we should expect to have some level of cancer always. These are probably about 15 per cent of cancers in the USA.

2. Some individuals are born with a genetic change in all cells that increases their risk of spontaneous cancer; these hereditary cancers probably account for no more than 5 per cent of cancer. There seem to be at least 3 hereditary forms of breast cancer, for example.

3. The genetic constitution of cells can be changed by environmental agents, notably chemicals, radiation, and viruses.

leading to induced cancers. This and the next category together may account for 80 per cent of cancer in the USA.

4. Some individuals are born with a genetic predisposition to environmentally induced cancer, e.g., white persons are more susceptible to sunlight-induced cancers than are black persons. We do not know how much "environmentally induced" cancer is occurring in susceptible persons. It could be a large fraction. There is a significant body of ongoing research dealing with mechanisms of susceptibility and identification of subjects at high risk.

5. The principal environmental agents that cause cancer in the USA are thought to be smoking (about 1/3 of cancer deaths, chiefly lung and bladder cancer), and diet (chiefly breast, colon, uterus, and prostate cancer). There is a strong correlation world-wide between the incidence of these latter cancers and animal fat consumption. Active programs of research and even dietary intervention are in progress.

Mechanisms:
See figs page 3

1. Some viruses cause cancer by carrying specific genes, called oncogenes, into the host cell. These genes constitute a critical alteration in the genetic constitution of the host cell. These viruses are very efficient cancer producers but they account for little or no human cancer.

2. Some related viruses cause cancer at a much lower rate. They lack oncogenes. They cause cancer by incorporating their genetic material adjacent to normal oncogenes of the host. The first category of viruses was probably created when members of this second category then escaped from cells carrying all or part of the host oncogenes with them.

3. Cancer can evidently be caused in some cases by directly altering the structure or the activity of host oncogenes without the intervention of viruses, by spontaneous or environmentally induced events. The detailed study of a rare cancer that occurs primarily in children, Burkitt's lymphoma, has been particularly informative.

4. Another class of cancer genes, which I call anti-oncogenes, has been identified through the study of hereditary cancers. From the study of two childhood cancers, retinoblastoma, an eye cancer, and Wilms' tumor, a kidney cancer, it has been demonstrated that the inherited mutations are the first steps on the paths to these cancers. The same changes occur in the target organs in the non-hereditary cases of these same tumors. A second event is necessary in both the hereditary and non-hereditary cases; it is the loss of the normal copy of the same gene on the other chromosome of the relevant pair.

5. Normal anti-oncogenes may be regulators of normal oncogenes, so the production of cancer by oncogene abnormality and by

39-154 O—84——8

loss of anti-oncogenes may entail the same ultimate mechanism.

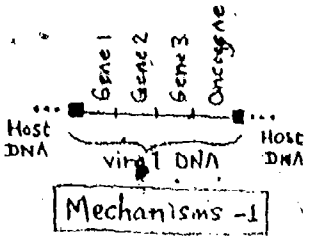
6. These two classes of genes, oncogenes and anti-oncogenes, are under intensive study, both for the elucidation of their roles in cancer and for their roles in the usual development of organisms. They obviously do not exist to cause cancer. They are present in a wide range of organisms; in fact, oncogenes have been found in yeast cells. It may even be that key information about them may derive from the study of organisms that do not acquire cancer.

Conclusions:

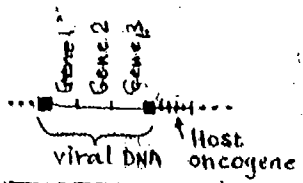
1. Some amount of cancer seems to result from spontaneous biological processes that are not avoidable.

2. Major changes in cancer incidence require new preventive measures. Current research on cancer causation may help reduce especially those cancers that are related to diet.

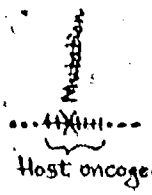
3. Major changes in cure rates require new therapeutic measures. Current research on cancer mechanisms may lead to such new measures.



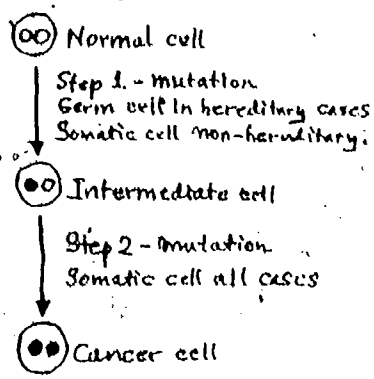
Mechanisms -1



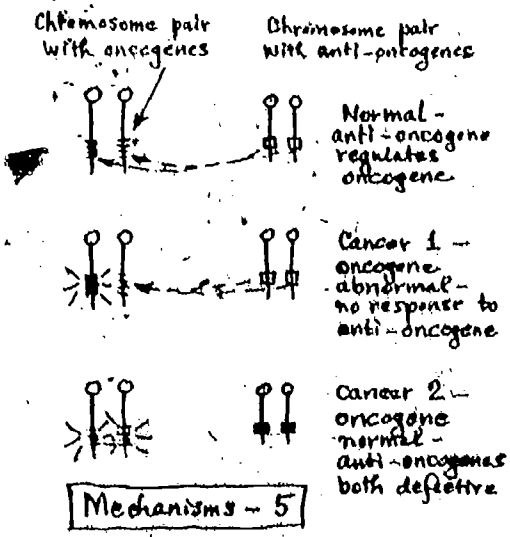
Mechanisms - 2



Mechanisms -3



Mechanisms - 4



Mechanisms - 5

Ms. OAKAR. That's very interesting and a cure for it gives a ray of hope that you're on the trail of this dreaded disease, in conquering it, it seems to me. Thank you very much.

Dr. Strax?

STATEMENT OF DR. PHILIP STRAX

Dr. STRAX. Thank you very much for the privilege of testifying. I find the previous speaker's remarks very exciting and I hope that we get somewhere with this. But I'm a very practical individual and I would like to talk about what can we do about breast cancer now, before we have found the real secret?

Breast cancer, let me recapitulate, is a disease women in this country fear most. We may not have an actual breast cancer epidemic at this time, but we surely have an epidemic of fear of the disease. Such fear has good reason for it and is based on the following, some of which you have already heard: Twenty years ago we used to say one woman in 20 would develop breast cancer. Today we know that one in 11 will be afflicted. Every 5 minutes or less a woman is diagnosed as having the disease, and every 15 minutes or less a woman dies from it.

The risk of getting the disease increases with age. A woman of 70 has at least 6 times the chance of having breast cancer diagnosed as a woman of 40. About two-thirds of the breast cancers are detected in women over 50. It is also, however, being found in increasing numbers in women under 40 or even under 35, as you have heard this morning.

At the present time, in spite of advances in treatment, not more than one out of three women with the disease is alive and well 10 years after diagnosis. Yet, we also know that with proper, complete, periodic examinations, early detection with modern techniques means that 9 out of 10 can be alive and free of disease 10 years after detection.

We don't yet know the cause of breast cancer, nor do we yet know how to prevent the disease. We also do not yet know how to cure breast cancer when it spreads beyond the breast. We do know that if we use our present know-how to detect the disease when it's localized to the breast and has not spread beyond it, 9 out of 10 women will be with us 5 or even 10 years later, compared to less than 50 percent if there is evidence of spread beyond the breast. And, most importantly, we have had a stationary death rate from breast cancer for the past 40 years. Just as many women die today from the disease in proportion to the population as did many years ago.

It's generally agreed among those of us involved in detection and treatment of breast cancer that the secret of long-term survival and cure at the present time lies in early detection. We must find the disease at the right time, before it has spread, when our present treatment methods are most effective. There are two hurdles to overcome. First, 90 percent of breast cancer is detected initially by the woman herself. In spite of much effort by the National Cancer Institute, American Cancer Society, and dedicated individuals in the private sector, most women have not learned, cannot learn, or refuse to learn, to follow through on breast self examina-

tion. Therefore, the majority of breast cancers found by women is late cancer, not early enough for a cure.

Even more importantly, the small, early, most curable cancer, and the one that we, as physicians, are most anxious to detect, is very often not at all palpable, and cannot be felt by the woman's hand, even when she's been trained to do so. It cannot even be felt in this early stage by the hand of the expert physician. Only the mammogram, a simple x-ray examination of the breast, can detect the disease before it can be felt. Breast self examination is just not enough at the present time. We must emphasize that we have definite proof from the large screening program for breast cancer detection of the Health Insurance Plan of New York, supported by the United States Public Health Service, that if we get women in for a breast examination when they're presumably well, we can save at least one-third more of those who develop the disease. That study, the results of which are still being followed, used techniques of examination which were not as efficient as those used today.

Our present techniques are more sensitive and more accurate and can produce much improved results compared to those of 20 years ago. Screening centers such as the Guttman Breast Diagnostic Institute in New York City, or the Strax Breast Cancer Detection Institute in Fort Lauderdale, FL, have clearly shown that women can be motivated to come in for examinations and that their breast cancers can be detected in an early, curable, stage, when a woman may not at all be aware of the problem and that detection of the disease at such a time means substantial saving of life from the disease. And you heard from one such woman this morning.

To reach such a goal on a widespread basis, we must develop motivation. Women need to become aware of the danger of breast cancer. They must learn that there is a remedy at hand, however complete, periodic, examinations, even when there are no signs or symptoms of breast conditions at all. Also, facilities for such examinations must be made available. More screening centers need to be developed on a public health basis. To do this, the problem of cost must be faced. Women will not come in to have examinations they cannot afford, when they're feeling well. Cost of examination must not be a deterrent. Means must be developed to make periodic examinations cost effective, through low initial cost, and support from public health authorities or third party payers.

It should be noted that we have excellent examples to prove that widespread mass screening for breast cancer can be done on a cost effective basis. At the Guttman Institute in New York City, complete examinations including palpation by physicians and modern mammography have been done on tens of thousands of women well over 100,000 women, as a matter of fact for the past 16 years, without charge to the woman. Today about 150 women are examined per day. Support has been given by patient donations, private sources, the American Cancer Society, and the National Cancer Institute. The actual cost to the Institute with large volume is about $25. This low cost is possible because of the large volume of 30,000 women who are examined per year.

At the satellite center in Fort Lauderdale, FL, called the Strax Institute, which was sponsored by Margie Mixson and Lieutenant

Governor Mixson, a nominal charge of $35 is made, with a volume of 10,000 women per year. Such a charge, plus some private donor help, can make the operation self-sufficient. Details of these operations are available in the attached reprint that you may get.

We do, however, need the dedication and cooperation of interested individuals and physicians. We are talking about a complete examination that includes clinical examination by a physician, plus the x ray. We depend, however, on a large corps of neighborhood volunteers who give freely of their time and effort to the cause, who give of themselves to help save the lives of women. There are physicians as well who are willing to contribute their time and expertise on a low-cost fee basis to help in this vital effort, and it should also be noted that large-scale mass screening programs for detection of early breast cancer are in operation in several foreign countries, based on the methods developed in this country.

You might be interested to know that I just heard of a center that's been set up in Liberty, MO, a small town, in a 202-bed hospital, where they are doing the complete examination at a cost of $25.10 and have examined over 1,000 women with this type of technique.

We now have the knowledge and means to give the women of this country the benefits of early detection and subsequent cure of breast cancer. We need to get as much support for such a program as possible, from third party payers or medicare, to help the financial burden. I respectfully suggest that a committee such as yours would be most helpful in this regard. With proper support we can do the job.

The essence of my presentation is that through programs such as the one at the Guttman and Strax Institutes, hundreds of early, unsuspected cancers, have been detected, and hundreds of lives have been saved. In addition, the cost of such detection has been far, far less than the cost of treating the disease in the advanced stage that would have been needed without mass screening. Early detection through mass screening can reduce the financial burden considerably and at the same time save many lives from the disease.

In short, the women of our country are faced with a serious problem: breast cancer. And the problem is getting worse. We also, however, have a solution which could save the vast majority of those afflicted. Someday we'll know how to prevent the disease or cure all those affected. Until that day arrives, let's use the means we have today safe, practical methods to save most of our women. All of us, public health authorities, third party payers, physicians, and the public at large, must cooperate in this effort to save the lives of women from this dread disease.

And finally, we need a strong push from a committee such as yours to get on with the battle. I am confident that we can and will win. Thank you.

Ms. OAKAR. Thank you very much, Doctor, and our last; but sometimes we save the best for last, Dr. Feller; our last witness is Dr. William Feller, and we're really delighted that you took time. I know how busy you are at Georgetown.

STATEMENT OF DR. WILLIAM FELLER

Dr. FELLER. Thank you, Madam Chairman. I think those of us of the scientific community are very, very impressed with the deep interest of this committee, in cancer research and we appreciate this opportunity to testify.

I will talk briefly commenting on the impact of basic areas of research on breast cancer control. I want to say that I speak as a representative of the American Cancer Society and a member of the scientific cancer research community. My present professional activities at Georgetown University School of Medicine include the teaching of medical students, breast cancer research activities, and the care of breast cancer patients.

Again, I think as everyone has emphasized here, Madam Chairman, that mammography is the gold standard of breast cancer diagnosis today. Dr. Strax did not mention the mortality figures which are available on the recent National breast cancer screening program. I discussed this with Dr. Costlow of the NCI and we looked at some of the figures. We can show that 92 percent of women could be cured of breast cancer if they had their cancers detected by mammography. In other words, in that group there were over 1,200 women whose cancers were picked up by mammography only and 92 percent of those were alive at 5 years, presumably cured.

I want to stress that mammography is certainly, at this moment, the way to go. As you know, the American Cancer Society, Madam Chairman, recommends that every woman over 50 have a mammogram every year.

Just to make a few comments, Madam Chairman, on the treatment controversy, as you heard today from Dr. Hubay and Dr. Crile. Obviously there is a controversy between the people who prefer the lumpectomy, radiation, verus the mastectomy. I don't think that this controversy is going to resolve easily. There was an article in the Wall Street Journal a few weeks ago about the controversy at Memorial Hospital in New York City and as you know, women, depending on who they see at that institution, will get different advice. But I think this type of controversy will go on for several years.

For women who elect to have a mastectomy, we at Georgetown University are doing immediate breast reconstruction. At Georgetown we've done 100 immediate breast reconstructions over the past 5 years, and we find that the results are as good as a delayed breast reconstruction.

Ms. OAKAR. You know, Doctor, let me tell you, a lot of women do not realize that they can have reconstructive surgery.

Dr. FELLER. Right.

Ms. OAKAR. They think that—and this is not a common notion among women, they think that if you have to have a mastectomy you cannot have a reconstructed breast done using your own skin. I've seen some of your, and as well as that of your colleagues in plastic surgery and it's just incredible. They are real breasts, you know.

Women don't know that. And they have this terrible fear of surgery and I think mutiliation, which I think we were talking about

earlier, not that that's necessary for everybody. But that is one of the real problems, that we haven't reached out enough maybe, some of us, and physicians that do this in some of the societies, to be more informative about what it is that's going on in the medical profession.

Dr. FELLER. Well, that is right. Hopefully some of the publicity from this hearing will point out the alternatives that women with breast cancer do have.

Ms. OAKAR. Right.

Dr. FELLER. There is the lumpectomy plus breast irradiation and as you have mentioned, also for women who elect mastectomy. Many centers, not a lot, but some centers in the country, are doing immediate breast reconstructions. We, ourselves, are giving scientific papers around the country and I think that we are beginning to see a national interest in immediate breast reconstruction.

I'd like to turn now to the two areas of research that I find very, very exciting, and I think that, again, we will see some breakthroughs, perhaps, in the treatment area in 5 to 10 years.

The two areas I refer to, Madam Chairman, are monoclonal antibodies and oncogene research. Let me first touch on monoclonal antibodies. In the past 10 years, new techniques of developing monoclonal antibodies have arisen and they now occupy a very prominent area of cancer research. I would say cancer research laboratories around the world are using monoclonal antibodies. And I would expect that within 5 years some of these techniques will find their way into clinical practice.

Let me just give you a few ideas of how we expect to see these.

Ms. OAKAR. Can you explain what that is?

Dr. FELLER. Yes. A monoclonal antibody is an antibody that is made in a test tube. You know, for years we used to make antibodies by injecting rabbits or goats or sheep and, indeed, many big hospitals had to have sheep farms or goat farms. And now we can make these very highly specific antibodies in test tubes. It's called the hybridoma technology, whereby we can take antibody-forming cells and fuse them to these cancer cells in a test tube which live forever.

Ms. OAKAR. Where do you get them from?

Dr. FELLER. They come from animals. In other words, we immunize a mouse or an animal with the antigen, with the human antigen. We then take the spleen cells, the so-called lymphocytes, from this animal, and fuse them to multiple myeloma cells. It's a fusion technique. And these cells, then, will live forever and they will produce huge amounts of monoclonal antibody.

The technique is so precise and we can make such large amounts of antibodies, it is like comparing a firecracker to an atomic bomb. That's the difference in principle. It's an entire new technique. It's revolutionized cancer research.

Well, let me just say how it's being used.

One thing that we are very excited about is a blood test for breast cancer. We have talked about blood tests for cancer and I think we are now on the threshold of that. We, at Georgetown, have used two monoclonal antibodies that we have obtained from the Netherlands Cancer Institute in Amsterdam, and preliminary studies, Madam Chairman, at our institution, with over 200

women, have shown this test is 95 percent accurate. And we are presently applying to the American Cancer Society to carry out a preliminary cancer screening study.

Let me just say a word how that would help us. If we could develop a blood test that was 95 percent accurate, and we could apply this to women across the country, we would then reduce the number of women who would require a mammogram by about 90 percent. We would anticipate that instead of having Dr. Strax screen 30 million women, we'd only have to screen, say, half a million women. It would lower the cost dramatically.

So, a blood test for breast cancer, and I think that this is truly possible within 5 years, will be a major achievement. I'm very optimistic.

Ms. OAKAR. You're applying for a grant to do some work on that?

Dr. FELLER. We are.

Ms. OAKAR. And what are your chances of getting it?

Dr. FELLER. We'll get the grant. We'll get the grant. Dr. DeVito knows about the work and Dr. Dick Rauscher, the president of the American Cancer Society. If I don't get the money I'll come back to see you, Madam Chairman.

Ms. OAKAR. That's right.

I think this is important.

Dr. FELLER. Well, the other thing on the monoclonal antibodies, and Dr. DeVito's group out there at the NCI are doing this, we can give these monoclonal antibodies intravenously and they will localize in human cancers, and we can make diagnoses of metastatic deposits.

Now, in breast cancer that's very important. As you know, we have to do axillary surgery. We are anticipating that with these monoclonal antibodies they will detect positive axillary lymph nodes for us without surgery. So, again, it would be a dramatic advance if that were possible. And these studies are going on at the present time in about a dozen centers in the world.

Ms. OAKAR. Are they going on in full force? Because we heard about the controversy about removing nodes and if you remove the nodes and they're good nodes, then you are not protecting your immunity, rather.

Dr. FELLER. Right.

Ms. OAKAR. When do you think that will take place?

Dr. FELLER. Well, I can speak.

I think there is—Dr. Schlom is at the NIH doing this work. I don't have all the details but I would gather that they are—I have been told they have successfully imaged several human breast cancer patients. The principle is established that monoclonal antibodies will localize in the human tissue, and I would expect this technique for imaging should be available within 2 to 3 years. I don't want to speak too specifically on that because I don't have exact details.

Ms. OAKAR. Right.

Dr. FELLER. But it is going on and Dr. DeVito, I was told, is spending over $60 million to $70 million a year on monoclonal antibodies. So, there is a very, very active interest. Now, a little farther down the road on monoclonal antibodies, but extremely exciting, is the fact that we can link these monoclonal antibodies to toxins or

to radioactive drugs and they then can act as a magic bullet. As you know, the cancer scientists have been talking about magic bullets, drugs that will only target on the cancer cell and will not harm the normal cell, and I think that now we are confident that those are within striking range.

There was an article in the Scientific American Journal, just this last month, on immunotoxins, and again this principle has been applied to animals, and we expect, Madam Chairman, that the immunotoxins, these magic bullets, will be tried in breast cancer patients probably in 3 years. That, again, is going very fast.

So, in summary, I think that the monoclonal antibodies are extremely exciting. I do think we will see them introduced within clinical practice, certainly on a trial or experimental basis, within 3 to 5 years.

Now, if I may, let me touch on oncogene research. As you know, as Congressman Gore's subcommittee 2 weeks ago, had a full hearing on oncogene research. And I was privileged to testify at that committee, Congressman Gore had 8 or 10 leading research, scientific experts, testify. And I want to summarize that for you.

First of all, I want to say that I think oncogene research represents the most dramatic breakthrough in cancer research in the entire century. I don't think there was a witness there who was not absolutely enthusiastic about the significance of this breakthrough. As Dr. Knudson said, we now have the know-how to understand how cancer occurs at the molecular level.

Now, I also want to stress, because it was stressed repeatedly, that we do not expect clinical results for at least 10 years. We need a lot of hard work.

But the point is that we now have a way of understanding how cancer occurs at the cellular level.

Ms. OAKAR. So that's a breakthrough.

Dr. FELLER. That is a dramatic breakthrough, the biggest in the century. And that has occurred within the last 5 years. And as you alluded to, that grew out of the special funding that Congress provided to the NCI in the early seventies for the virus cancer work. And I want to touch on special funding.

But I do think that within 10 to 15 years the oncogene research, that knowledge will come into the clinic. And I did predict at that hearing, and I will predict here, that if we follow these leads, it is quite possible that we can expect to cure 90 percent of all cancers by the end of the century.

I am surprised that some of my colleagues haven't criticized that prediction, but I really stand behind it. I think that if the oncogene breakthrough in basic research could be applied to patients a 90 percent cure rate in 15 years is possible.

Let me just say a few words about the oncogene concept. Dr. Knudson touched on it.

First of all, it grew out of the cancer virus work. As you know, scientists have been interested in cancer viruses for many years. It goes back to the chicken sarcoma work of Dr. Peyton Rous at the turn of the century. His work finally led to the concept of oncogenes, as Dr. Knudson alluded to, and now we have isolated several specific oncogenes from human cancers.

I want to say, as Dr. Knudson did, that all of us carry oncogenes in our cells, as part of our genes. There are about 20 of these oncogenes which have been identified. There are probably about 10 more that we have not isolated. And we now are aware that when these oncogenes are inappropriately expressed we have a cancer.

Let me say a word about how oncogenes might be applied in the next 10 years to the clinical world. First of all, in cancer risk prediction. Now, as you've alluded to, and as Dr. Knudson has alluded to, we know, Madam Chairman, that certain women are at a high risk for breast cancer. As you know, we've talked about family history, as an example.

Ms. OAKAR. I am at high risk because my mother had it. Right?

Dr. FELLER. Right.

Ms. OAKAR. Most women are kind of high risk, aren't they, because somebody in their family had breast cancer somewhere along the line?

Dr. FELLER. Right. Now, if the oncogene concepts are right, we would be able to take just a few of your cells or even a blood test, or maybe a small needle biopsy of your breast tissue. We would analyze this and we could give you an accurate risk assessment. That means if you come to me and I do this study, I could say, "Madam Chairman, you have a 60-percent chance of developing breast cancer." Somebody else might come and I might say, "You have only a 2-percent chance."

Now, you say, "Well, what do you do with these high risk people?" Well, we go back to the chemo prevention, the diet, there are a variety of strategies that we can use. You might even want to consider the surgical removal of your breast.

Let me go on to cancer diagnosis. We have developed already, we think, a reasonably accurate test. But we know that all oncogenes produce an oncogene protein. That is, the oncogene acts to cause cancer in the cell by producing a very specific oncogene protein.

Some cancer scientists believe that these oncogene products are shed in the blood and, again, I think that we're looking at another possible source of cancermakers for very early blood tests.

And finally, and again this is down the road 10, 15, 20 years, but we expect whole new treatment strategies to evolve. What we now know is that the cancer cell is only a cancer as long as the oncogene is expressed. And if sometime in the next 5, 10, or 15 years some scientist learns how to switch a gene off, with a simple measure, they can cure cancer, really, without surgery or without harmful drugs or without radiation. I know this sounds like a fantasy.

Ms. OAKAR. Oh, no.

Dr. FELLER. We are predicting that if we learn to switch off the oncogenes, we will have an entirely new method of treating cancer.

Well, I'd like to just end by saying to you, as you have indicated, of course, the Congress is very interested in the field of cancer research. I was very delighted to hear Senator Pepper's remarks about 1937 and the $500,000 and I do agree with Senator Pepper. I think perhaps the American people and the Congress have got to be more bold in spending money. I think I have heard repeatedly today we spend a great deal on missiles and on military preparedness, and we're not prepared to spend more than a billion dollars a year on cancer research. And I would respectfully suggest, Madame

Chairman, that the Congress look into accelerated funding. You did that in the early seventies, you gave cancer scientists extra money, you gave the National Cancer Institute extra money for the virus program, and I would suggest that at the present time you ask the NCI, Dr. Devita, "Could you use another hundred or $200 million a year for oncogene research?"

We are on the threshold for, really, a dramatic revolution. And I think if this country survives to the end of the century, and I think that we will,—people will look back and see our contribution, our effort, in cancer research as one of the major contributions that this Republic has made to the Western World. So, I urge you to really consider expanded funding for oncogenes.

Thank you.

[The prepared statement of Dr. Feller follows:]

PREPARED STATEMENT OF WILLIAM F. FELLER, M.D., PH.D., ASSOCIATE PROFESSOR OF SURGERY, GEORGETOWN UNIVERSTIY, WASHINGTON, DC

Mr. Chairman and Members of the Subcommittee:

I appear before your Subcommittee today to speak to the subject of present day breast cancer research and its implication on the control of breast cancer in the United States. I speak as a representative of the American Cancer Society and a member of the scientific cancer research community. My present professional activities at Georgetown University, School of Medicine, include teaching of medical students, breast cancer research activities, and the care of cancer patients. I have been a professional Volunteer of the American Cancer Society for fifteen years and currently am the President-Elect of the District of Columbia Division of the American Cancer Society. I shall try in these statements to summarize the current clinical status of breast cancer in reference to current diagnostic and treatment modalities. I shall also comment on the possible impact of two basic areas of cancer research on the future clinical control of breast cancer. These two areas of basic cancer research are : (1) oncogene research, (2) monoclonal antibodies.

Current clinical status of breast cancer diagnosis and treatment in the United States

Breast cancer is the most common type of cancer in women today. It accounts for 25% of all cancer occurring in women. In 1984, there were about 115,000 new cases of breast cancer in

the United States, almost all diagnosed in women. The American Cancer Society estimates that 38,000 American women will die of breast cancer in 1984. Epidemiologists estimate that one of 11 American women will develop breast cancer during their lifetime.

The five-year survival or cure rate of breast cancer is directly related to the stage of the disease when it is first treated. If the cancer is localized to the breast, about 87% of cases will be alive at five years, if it has spread to the regional lymph nodes, the five-year survival is generally less than 50%. A recent study of women whose breast cancers were first detected by mammographic screening showed a 5 year survival of 92%. Breast cancers detected by mammography are generally very early cancers. These highly favorable survival figures show the critical importance of early diagnosis. Many of these women with an early diagnosis can be treated by a breast saving operation known as lumpectomy. The cosmetic results in this breast conserving operation are generally excellent.

Early diagnosis of breast cancer

Regular breast examination by women themselves and trained professionals plus annual mammography for women over 50 years of age would virtually insure early diagnosis for most women. Mammography is the gold standard of breast cancer diagnosis. No other known noninvasive diagnostic method has achieved the high

accuracy of mammographic diagnosis. Properly done and interpreted by experienced radiologists, mammography can achieve an accuracy rate of 85% even with very small cancers. Besides its effectiveness in screening women without symptoms, mammography is recognized as a valuable diagnostic technique for women who do have findings suggestive of breast cancer. Once a breast lump is found, mammography can help determine if there are other lesions in the same or opposite breast which are too small to be felt. All suspicious breast lumps should be biopsied for a definitive diagnosis -- even when the mammogram is described as normal.

The American Cancer Society recommends a mammogram every year for asymptomatic women age 50 and over, and a baseline mammogram for those 35 to 39. Women 40 to 49 should have mammography every 1-2 years depending on physical and mammographic findings as well as other risk factors. In addition, a professional breast examination is recommended every three years for women 20 to 40, and every year for those over 40.

Other imaging techniques such as thermography (heat patterns), ultrasound,diaphonoscopy (inspection with a high intensity cold light beam) are currently being studied for their possible effectiveness in detecting early breast cancer. At present, these techniques have not proven to be as effective in early diagnosis as mammography. Although mammography came under widespread criticism about ten years ago, because of the possibility that the diagnostic radiation itself was a cancer-causing agent, careful studies over the past ten years have generally vindicated its

widespread clinical use. Certain clinical precautions have evolved during this period. First and foremost the use of very low radiation doses for most mammographic studies have become routine in most radiological facilities. Today most clinical facilities can achieve excellent results with radiation doses less than 0.5 rads per examination. Secondly, the use of mammography in younger women under the age of 30 or 35 has generally been abandoned. Mammography in younger women carries a higher cancer-causing risk and is generally not accurate. In summary, most radiation studies have shown that the benefit of early diagnosis far outweighs any carcinogenic risk especially in women after the age of 50.

Present treatment alternatives

Generally, two methods of treating localized breast cancer are used in the United States today. The most widely used primary treatment is a total mastectomy with an axillary dissection -- known to most clinicians as a modified radical mastectomy. The important chest wall muscle, the pectoralis muscle, is generally totally preserved. A second method of primary treatment coming into vogue in many large centers in the USA the last 10 year is lumpectomy plus breast irradiation. This treatment modality is used primarily for small or early breast cancers. This method conserves most of the breast tissue and is appealing to women who want a very good cosmetic result.

If examination of the axillary lymph nodes in either treatment modality shows that they contain cancer cells, it is generally recommended that those women have adjuvant chemotherapy for six months following surgery. Several long term studies have confirmed improved survival rates in lymph node positive women receiving adjuvant chemotherapy. The use of adjuvant chemotherapy of breast cancer appears to be moving in the following directions: (1) more intensive treatment by increasing the number of drugs or dosage levels; (2) shorter treatment periods, in the range of six months; (3) the addition of hormonal manipulations such as tamoxifen; (4) earlier treatment, pre- or perioperatively in some cases; and (5) individualizing treatment by risk subgroups, such as treatment of some high risk node negative patients. There are over 50 well organized studies continuing in the area of adjuvant chemotherapy of breast cancer, including a number of studies with "no treatment" control groups.

Women who come to primary treatment with more advanced disease may be advised to undergo more extensive surgery or to have some combination of local irradiation, chemotherapy and extensive surgery. The treatment of locally advanced breast cancer continues to be a major therapeutic challenge.

It should also be noted that women who have a mastectomy as their primary treatment often have breast reconstructive procedures by means of plastic surgery. The reconstructive surgery may be done immediately or simultaneously with the mastectomy or it can be done some months later. The use of the immediate breast

reconstruction is receiving wider attention in major cancer centers in the USA. At Georgetown Hospital we have carried out mastectomy and immediate breast reconstruction on 100 women with early breast cancer during the past five years. Our analysis of the curative results indicates this method is as good as mastectomy alone. Additionally, our cosmetic results have been excellent and the incidence and depth of post operative depression has been much less when we use immediate breast reconstruction.

Which of these two primary methods of treating breast cancer to use in a given case of early breast cancer remains controversial. While many clinicians especially surgeons have remained skeptical of the curative results of the breast conserving lumpectomy, a number of carefully controlled studies have shown that for early breast cancer, i.e. cancers less than 2 cm. in diameter (about one inch in size) the 5 and 10 year curative results are the same. The possible long range side effects of breast irradiation are unknown and could be troublesome although not life threatening.

The most widely respected study comparing the two methods comes from the National Cancer Institute of Milan, Italy.(1) Dr. Umberto Veronesi who is perhaps the world's most experienced breast surgeon has published the results of his randomized study of over 700 women with breast cancer. Half or 350 women had a radical mastectomy as the primary treatment while 350 other women randomly selected had one quarter of the breast removed surgically, plus an axillary dissection and breast irradiation. Eight years

after the conclusion of this study the curative results of the two matched groups are identical. It should be stressed that all the women in the Milan study had early breast cancer, i.e. tumors less than 2 cm. All women with cancer positive axillary nodes received adjuvant chemotherapy. Other studies from cancer centers in France, England, Canada and the USA have generally confirmed the Italian results. Well over 10,000 women in the Western world have been treated for breast cancer with lumpectomy and breast irradiation. In certain centers in France this method has been used since 1960.

A recent article[2] in the Wall Street Journal (June 13, 1984) highlighted the intensity of the treatment controversy. The newspaper story focused on the difference of opinion of two highly respected cancer physicians at the world famous Memorial Sloan Kettering Cancer Center in New York City. The Wall Street Journal article noted that Dr. Samuel Hellman, a cancer radiation expert, who just became the physician-in-chief of the Memorial Hospital is a prime advocate of the lumpectomy plus breast irradiation approach to the treatment of early breast cancer. Prior to coming to Memorial, Dr. Hellman supervised breast cancer treatment at the Harvard Medical School's Joint Center for Radiation in Boston. Dr. Hellman's experience with over 600 women have convinced him that lumpectomy and breast irradiation for early breast cancer is as good as mastectomy. The Wall Street Journal article noted that Dr. Jerome Urban, a highly experienced breast surgeon at the Memorial Cancer Center is critical of Dr. Hellman's statistics. Dr. Urban is quoted as

saying "Published reports from France as well as the U.S. indicate a recurrence rate of 15% to 18% among women treated with radiation 10 or more years ago." Dr. Urban still recommends a mastectomy for women with early breast cancer. Locally at Georgetown University Medical Center we also see similar differences of opinion regarding the best treatment for early breast cancer among our cancer physicians and breast surgeons. Today it is common that women will get conflicting advice about treatment preference in the same cancer center.

In the next week or so a large American study will be published in a leading American medical journal about the results of a clinical study launched in 1976 involving hundreds of American women with breast cancer from 28 medical centers. This study compared the curative results of women assigned randomly by a computer to three treatment modalities: (1) mastectomy (2) lumpectomy alone (3) lumpectomy plus breast irradiation. While rumors about the results of this large study have circulated in medical circles for several months, an extremely tight lid of secrecy has been kept on the details of this medical study. It is not generally believed that this large American study will settle the treatment controversy.

Implications of present cancer research on breast cancer control

Two major areas of cancer research will likely impact on the clinical management of breast cancer sometime within the next

five to ten years. The two cancer research areas of relevance to breast cancer are oncogene research and the use of monoclonal antibodies in diagnosis and treatment. These two basic science research areas have emerged into scientific prominence during the past five years. Of the two fields, monoclonal antibodies will most likely impact the clinical management of breast cancer first. Indeed, human studies with monoclonal antibodies for diagnosis and treatment of breast cancer are currently underway in several cancer centers. Preliminary results of these monoclonal antibody studies on human subjects should be available to the scientific medical community within one year. Research on monoclonal antibodies goes back to the discovery of the hybridoma technology by Kohler and Milstein at Cambridge University in 1976.(3) Today, the use of monoclonal antibodies in cancer research is world wide and monoclonal antibody techniques have opened several possible new methods of diagnosis and treatment. Oncogene research is not as far advanced in regards to clinical applications as monoclonal antibody techniques. However, the longer range implications of oncogenes could be far more dramatic. It is likely that altogether new and revolutionary clinical strategies will evolve from oncogene research before the end of the century. However, it should be stressed that new clinical therapeutic strategies are not likely to appear for at least 10 years.

Monoclonal antibody research and its application to breast cancer diagnosis and treatment

Presently, there are about 30 human breast cancer related monoclonal antibodies in existence in Western cancer research laboratories. A number of these antibodies have been shown to be capable of localizing in human breast cancer cells growing in test tubes or in experimental animals. A few localization studies have been carried out in human patients. A Workshop Conference on monoclonal antibodies and breast cancer is being planned for November 8 and 9 in San Francisco. It is expected that about 50 scientists will present papers summarizing the present state of knowledge on monoclonal antibodies and breast cancer at this meeting. Monoclonal antibodies appear promising in three clinical areas: (1) serum assays (blood tests for breast cancer) (2) cancer imaging in the patient (3) treatment.

Serum assays: Preliminary work in our cancer research laboratory at Georgetown University using two monoclonal antibodies developed in the Netherlands Cancer Institute in Amsterdam, has resulted in a possible blood test for early breast cancer detection. This test is 95% accurate in our hands. Extended clinical studies are now in progress. The Dutch monoclonal antibodies detect differentiation antigens shed by cancer cells in the blood. We are hopeful that our monoclonal antibody blood test can be applied to clinical screening. Presently, we are applying to the American Cancer Society for a grant to carry out a small preliminary breast

cancer screening study. The results of this preliminary study should be available within 6 months. It is likely that accurate blood tests for breast cancer will be available within five years.

Imaging: Breast cancer specific monoclonal antibodies can be conjugated to radioisotopes. These conjugated antibodies can then be given to a patient intravenously and the immune conjugates will localize in breast cancer cells where ever they are located in the body. Using a highly sensitive radioscanner "image" pictures can be obtained of internal metastatic cancer tumors. These imaging techniques could be used to survey axillary lymph nodes for cancer cells without surgery or detect other types of metastatic disease.

Treatment: Several studies have shown that toxins, radioisotopes, and drugs can be coupled to monoclonal antibodies and that these immune antibody conjugates may be useful in treating cancer. Animal studies have demonstrated that cancer cells can be selectively killed with antibody conjugated toxins or immunotoxins. The key idea here is to link a toxin agent to a monoclonal antibody thus creating a "magic bullet" that could kill targeted cancer cells but leave normal cells unharmed. At the present time it appears that the major research thrust is in the field of immunotoxins although studies with radioisotope conjugates are also being carried out. The long term challenge is to develop immunotoxins

into a new family of chemotherapeutic agents. Tests of immunotoxins have been done in animals, with some reports of tumor regression or reduction in size. Michael Bernhard of the National Cancer Institute[4] and his colleagues treated liver carcinomas in guinea pigs with an immunotoxin consisting of a diphtheria toxin component linked to a monoclonal antibody. A single dose of the immunotoxin led to tumor regression although the tumor was not completely eradicated. It now appears likely that a few specific immunotoxins for human breast cancer will be available within five years. Clinical trials with some of these breast cancer immunotoxins will likely be initiated before the end of the decade.

Oncogene Research

On June 6, 1984, I testified before the Subcommittee on Investigations and Oversight of the House Committee on Science and Technology on the subject of oncogene research. Congressman Gore's Subcommittee heard from 8 to 10 leading scientific experts on the implications of present oncogene research trends on the control of cancer in the U.S.A. All witnesses agreed that the discovery of the oncogene and the subsequent oncogene theory of cancer causation is perhaps the most important research breakthrough of the century. All of the experts however, cautioned that clinical results from this laboratory breakthrough should not be expected for at least 10 years and more likely 15 - 20 years.

The discovery of oncogenes represent a conceptual breakthrough but the application of this knowledge to cancer control still will require intense and difficult research studies for several years. Some of the witnesses raised the question of an accelerated funding for this kind of cancer research. It seems likely that the Gore Subcommittee will explore the issue of accelerated funding further. Let me summarize my previous testimony on oncogene research and attempt to relate it to breast cancer. I will also try to suggest some ways that oncogene research could be targeted towards the problem of breast cancer control.

Overall Significance of Oncogene Research

The discovery of oncogenes and their action in the cancer cell has been the single most important development in modern cancer research studies. The discovery of specific cancer causing genes in human and animal cancer cells represents a dramatic conceptual breakthrough which will change the course of current cancer research. Scientists have discovered a new and precise way of looking at the causative mechanisms of cancer at the cell level. The oncogene or cancer gene concepts grew out of the vast body of scientific knowledge which accumulated with the studies of RNA tumor viruses over the past 70 years. The discovery of oncogenes can be likened to the discovery of the tubercle bacillus by Koch in 1880. This discovery of the causative agent of tuberculosis laid the foundation of modern bacteriology and led to

techniques for early diagnosis and ultimately antibiotic treatment of tuberculosis.

Today, scientists have discovered the biological unit - the oncogene - whose improper activity causes cancer in animals and in man. There are about twenty of these onpogenes that play a role in the causation of cancer.

We are now beginning to dissect the molecular events leading to the malignant transformation of a normal cell. The major molecules acting in the cancer process and the outline of how these molecules interact one with another in the malignant process are already in view and the exact details of these biochemical processes are rapidly being developed.

Development of the Oncogene Concept

The story of oncogenes really goes back to 1911 when Dr. Peyton Rous[5] identified a virus - then called a cell free filtrate - from a chicken sarcoma. He showed that he could transmit or initiate a new cancer in chickens with this cell free preparation. Thus, RNA tumor virology was born. In the 70 years since then, the Rous sarcoma virus has become the most widely studied animal cancer virus. Eventually, the cell free preparation was shown to contain an RNA tumor virus. In 1970 Duesberg and Vogt[6] showed that the Rous virus contained a cancer gene or oncogene. Subsequent work clearly showed that the oncogene in the Rous sarcoma virus caused cancer to develop in susceptible

cells. Defective Rous sarcoma viruses without the cancer gene did not cause cancer. The cancer gene was isolated in 1976 by Stehelin, et.al.[7] (Bishop's laboratory).

Other types of RNA tumor viruses were discovered during the intervening years. In 1936 Bittner[8] isolated a "factor" in mouse milk that caused breast cancer in mice. Ludwig Gross[9] in 1951 demonstrated that mouse leukemia could be transmitted by a cell free filtrate. By the mid 1960's RNA tumor viruses had been isolated from a wide variety of animal tumors. Such diverse tumors as mouse breast cancer, mouse leukemia and sarcoma, bovine leukemia, cat leukemia and cat sarcoma - all of these cancers were shown to be causally related to RNA tumor viruses. Although extensive attempts to isolate a human RNA cancer virus had been made by 1970, no human RNA tumor virus had been isolated at that time. Finally in 1981, Robert Gallo[10] of the National Cancer Institute isolated a human RNA tumor virus from several patients with a certain type of leukemia (human T-cell leukemia).

The discovery and identification of the Rous sarcoma virus oncogene was a pivotal event in oncogene research. It clearly established that the presence and activity of a single gene in an animal cell could cause cancer. The identification and isolation of the "transforming cancer protein" by Brugge and Erickson[11] in 1977 further strengthened the oncogene concept. Many activated genes initiate a process and provide the necessary information for the ultimate development of a specific protein. These gene encoded proteins are generally enzymes or structural proteins which are

necessary for the normal maintenance of cellular processes. The "transforming cancer protein" of the Rous sarcoma virus was found to be changing some fundamental property of the normal cell so it became a malignant cell. The detailed molecular events of the malignant transformation of a cancer cell could now be studied with this model. By 1980 the outline of the present oncogene theory was clearly in place. It was known that many, though not all, of the animal RNA tumor viruses could transform certain types of normal cells into cancer cells in the test tube. Like the observation of Duesberg and Vogt with the Rous sarcoma virus, it was observed that all of the "test tube transforming" RNA tumor viruses carried a single gene that causes cancer. These viral type oncogenes were the responsible agents for the malignant transformation seen in the test tube.

The molecular biology of the RNA tumor viruses and how they act inside of infected cells was also well known by 1980. RNA tumor viruses belong to a class of viruses called retroviruses. The genetic information of these types of viruses is carried in the form of RNA and additionally they carry an important enzyme, reverse transcriptase, in the virus packet. During their life cycle inside of a cell, the RNA genes are copied into DNA, and this new DNA segment or gene is integrated into the cell's genes. If the RNA tumor virus carries an oncogene, that gene is incorporated into the cell's genetic apparatus and will generally be activated and expressed. The expression of this newly acquired oncogene by the cell causes the cell to become malignant. As long as the cancer gene is active, the cell is malignant. If the gene is switched off

the cell loses its malignant character and becomes a normal cell. But the critical question was, where did the oncogene itself come from? Was it always a viral derived gene or could it have originated in animal cells? The final answer - now clearly established - has shown that the viral oncogene was really a copy of a cellular gene - a proto-oncogene. Thus, today we know that cancer genes are normal components of all animal cells.

Cellular Oncogenes

How did we get scientifically from viral oncogenes to cellular oncogenes? In 1969, Huebner and Todaro[12] had noted that leukemia in mice could be transmitted through the germ cells and because of this observation they postulated the existence of a "cellular oncogene". They postulated that most if not all animal cells had cellular oncogenes which could under the appropriate circumstances cause cancer. It was the work of Stehelin, Varmus, Bishop and Vogt[13], in 1976 that clearly showed that cells of virus free birds (chicken and quail) contain cellular oncogenes identical to the viral type oncogenes seen in the Rous sarcoma virus. These findings of cellular cancer genes highly related to viral type cancer genes were soon extended to cells of other animals - cells of all vertebrate species. Thus these critically important studies established the central thesis of the oncogene theory: Oncogenes are normal components of all animal cells. How these cancer genes act to cause cancer has been broadly worked out the past six years.

Today there is a general outline of an oncogene mechanism. Several details are missing and the precise mechanisms of control are unknown but the protein products encoded by several cancer genes are known and their function in some malignant cells has been defined.

Cellular oncogenes demonstrated by direct gene transfer

Recently (1979) human cancer genes have been isolated using more direct gene transfer methods. Three American laboratories have accomplished these direct cancer gene isolations. (Weinberg, MIT; Cooper, Harvard Medical; Wigler, Cold Springs Harbor). Using the methods of gene cloning, Weinberg and his colleagues[14] extracted single genes from human cancer and transferred these single cancer gene units to normal animal and human cells. These transferred cancer genes caused the normal cells to become malignant. It was quickly noted that many of these oncogenes isolated from nonviral type animal cancers or from human cancers were almost identical to the viral type oncogenes of the RNA tumor viruses. Thus, using data obtained from two diverse technologies, i.e. viral oncogene probes and direct gene transfer, it has been established that human cells contain several cancer causing genes. These genes are either mutated or have become switched on inappropriately in human cancer cells.

Present Concepts and Postulates of the Oncogene Theory

1. There are about 20 known human cancer genes. Probably 10 or 20 more exist but have not been identified.
2. " 19 viral type oncogenes have been identified. Cellular cancer genes related to most of these have been found in normal cells of man.
3. Cancer genes play an important role in many if not all normal cells at some point in their development. Their activity in normal cells seems largely related to the growth signal systems of normal cells. Many normal cells are known to express or exhibit oncogene activity.
4. Cancer genes follow classical Mendelian Laws in general.
5. Most cancers probably express abnormal activity of at least two oncogenes. A recent study of oncogene expression in "fresh" human tumors revealed the expression of four oncogenes in most cancers studied. Some cancers exhibited expression of seven different oncogenes.
6. Oncogene expression has been detected in some "fresh" human cancers as well as in human cancer cell lines.
7. The protein products of several (5 or 6) oncogenes have been identified and isolated. Two types of function have been assigned to oncogene proteins: Several oncogenes encode a protein that is a tyrosine specific kinase. This enzyme may function to regulate growth factor receptor status. Some cancer genes encode or produce a protein that binds to DNA and could thus act to regulate or control

other genes. Two oncogene protein products are growth factor receptors (or parts of a growth factor complex).

8. Two mechanisms probably account for the conversion of normal acting proto-oncogenes into cancer causing genes:

(1) A carcinogen stimulates the cancer gene into greater activity and thus allows the gene to produce a much higher level of protein product than normal. (100 fold increase in oncogene product has been reported in some cancers).

(2) A carcinogen "mutates" or damages the "normal oncogene" and thus a structurally abnormal protein product is formed which loses its normal cellular function. Both mechanisms probably occur. Most cancer genes probably operate by inducing higher levels of protein products. (C-ras Ha), a type of oncogene, is known to contain a single point mutation (damaged or changed DNA sequence). How prevalent this gene or other "mutated" type cancer genes are in human cancer is unknown.

Future Research on Oncogenes

It is highly likely that the work on oncogenes will open several new strategies for cancer diagnosis and treatment. Within ten years new approaches to cancer diagnosis and therapy are likely because of the oncogene breakthrough. Currently, scientists are predicting that oncogene knowledge will be helpful in three areas

of clinical cancer management: (1) cancer risk prediction (2) cancer diagnosis (3) cancer treatment.

Cancer risk prediction: Today we are aware that certain individuals are at a much higher risk than normal individuals for developing cancer. Data obtained from the study of a group of very rare hereditary cancers has led to the idea that there are very specific genes related to cancer susceptibility. These genes determine the cancer risk of any given individual. Whether these cancer susceptibility genes are actually oncogenes or more likely genes which can switch oncogenes on is unknown. Some cancer scientists believe that we can soon develop clinical techniques for gene analysis which would allow us to detect activated susceptibility genes or activated oncogenes. Individuals with activated susceptibility genes or activated oncogenes would be at very high risk for developing cancer. Individuals in whom these genes were turned off would be very unlikely to develop cancer. If accurate cancer risk assessments could be made on specific individuals, this achievement could have a far reaching impact on cancer control. Individuals known to be at a very high risk for specific types of cancer could be advised to use cancer chemoprevention drugs or special diets and more importantly have annual cancer diagnostic tests. Rational removal of high risk normal tissue could also be implemented, i.e. subcutaneous mastectomy. The underlying principle in all of these approaches is that a genetic change - an activation of a specific gene - can be

identified by the use of special molecular oncogene probes. The presence of a specific activated gene would specify a predisposition to malignancy.

Cancer diagnosis: Highly sensitive reagents for detecting the presence of oncogenes and oncogene protein products are already available. The first attempts to classify human cancer according to their oncogene characteristics has been recently published (Science, April 20, 1984)[15]. If cancer patients shed oncogene protein products in their blood these could be used to detect cancer at a very early stage. Present day monoclonal antibody detection techniques are extremely sensitive and could possibly detect very small amounts of oncogene products that might be shed in the blood of cancer patients. Monoclonal antibodies for detecting oncogene protein products should be generally available to the scientific community within two years. Clinical surveys of cancer patients blood for the presence of oncogene products will likely be undertaken in several cancer centers within one to two years. We have already initiated plans for such a study in our laboratory at Georgetown University.

Cancer treatment: Can oncogene derived knowledge of the molecular events occurring at the cellular level in carcinogenesis lead to new treatment strategies? The most fundamental question in this regard is: Can we devise strategies to switch off cancer genes? From animal studies we know that if we switch off or repress the activity of an oncogene, that cell is no longer malignant. The switched off cell behaves as a normal cell. The mechanisms for

39-164 · O—84——10

turning off gene activity are poorly understood at present. If the switch off strategy eludes us, then strategies to neutralize or block the action of oncogene products seem feasible. Since the activated oncogene acts on the cell through a protein product intermediary, interference with this "cancer causing protein" could be deleterious to the cancer cell. Several new treatment strategies will undoubtedly be developed over the next ten years based on the molecular knowledge resulting from oncogene studies.

Application of oncogene research to human breast cancer

Several lines of evidence suggest that breast cancer in women is related to the expression of specific oncogenes. Of prime importance is the fact that the oncogene theory itself postulates that specific oncogenes are expressed in all animal and human cancers. Secondly, direct evidence of oncogene expression was presented in a recent report by Slamon et. al.(15) in Science on April 20, 1984. These investigators examined tumor tissue from four patients with breast cancer for oncogene expression. All breast cancer specimens had some evidence of oncogene expression. Most human cancer tissues showed expression of at least 5 different oncogenes.

A third line of evidence that oncogenes are of critical importance to human breast cancer is the strong similarity of human breast cancer to mouse breast cancer where specific oncogene expression is believed to occur. Indeed, there is some evidence that a type of RNA tumor virus may be involved in the

etiology of human breast cancer. A specific nontransforming RNA tumor virus is known to play a critical etiological role in mouse breast cancer. Human genes related to the genes of the mouse breast cancer virus have been detected in human breast tissue. These genes could promote or switch on oncogenes in the human breast cell. There is evidence that the mouse breast cancer virus causes cancer in that animal by activating a cellular oncogene (16). In summary, oncogenes probably play a very significant role in the causation of human breast cancer. The accumulation of knowledge about oncogenes and how they operate to cause human cancer should have a profound impact on the ultimate management of breast cancer.

Recommendations:

I suggested at the Gore Subcommittee Hearings on June 6, 1984, the possibility of increased or accelerated funding in the area of oncogene research. I raised the question of whether increased funding in this area of cancer research might speed up the delivery of useful clinical strategies based on oncogene derived knowledge. A precedent for accelerated funding of targeted types of cancer research was set by the Congress in the late 1960's. Indeed, the Special Cancer Virus Program of the National Cancer Institute is a prime example of a successful "accelerated funding program". Between 1970 and 1976 the amount of monies spent on virus cancer research quadrupled ($21 million to $85 million). By 1976 over 100 million dollars was spent in the United States annually on virus cancer research. Dr. Fischinger's testimony at the Gore Subcommittee Hearing indicated that the amount of money spent on

"pure oncogene research" in 1983 was 36 million dollars, about 3.7% of the total National Cancer Institute's budget.

If the Congress were to consider accelerated funding in this field, I would recommend a somewhat broader targeted category - that of the regulation of gene expression. Oncogene research today is largely one facet of gene regulation. Advances in the general knowledge of gene regulation would likely be very helpful to oncogene research. Conversely, oncogene research appears to be on the "cutting edge" of the field of gene regulation. Perhaps, the Congress can develop data on the resources presently allotted to the overall field of gene regulation research. Increased funding in this area of biological research would not only speed up oncogene research but yield broad benefits to society in many fields.

I would again ask the Congress to consider accelerated funding in the field of oncogene and gene regulation research. I would suggest the Congress ask three scientific groups to develop position papers on the question of accelerated funding to guide the Congress in its deliberations on this question. Specifically, the National Cancer Institute, the National Academy of Sciences and the American Cancer Society could be asked to present feasibility studies of accelerated funding to the Congress. On behalf of the American Cancer Society we would be willing to consider funding such a feasibility study and, if carried out, to present it to the Congress.

Thank you ladies and gentlemen for the opportunity to present my views on breast cancer research and the possible implications of present research activities on breast cancer control.

References

1. Veronesi, U., Saccozzi, R. et. al., Comparing Radical Mastectomy with Quadrantectomy, Axillary Dissection, and Radiotherapy in Patients with Small Cancers of the Breast. New England Journal of Medicine 305, 6-11, 1981.

2. Bishop, J.E., Medical Debate: Controversy Intensifies over the Best Method to Treat Breast Cancer. The Wall Street Journal, July 13, 1984.

3. Kohler, G. and Milstein, C., Derivation of Specific Antibody - Producing Tissue Culture and Tumor Lines by Cell Fusion. Europ. Jour. Immunol.: 6, 511-519, 1976.

4. Bernhard, M. Referred to his study in an article entitled, "Immunotoxins" by R. John Collier and Donald A. Kaplan. Scientific American 251,56, 1984. reference on page 64.

5. Rous, P., Transmission of a malignant new growth by means of a cell-free filtrate. JAMA 56: 198, 1911.

6. Duesberg, P.H., and Vogt, P.K. Differences between the ribonucleic acids of transforming and nontransforming avian tumor viruses. Proc. Natl. Acad. Sci. USA, 67: 1673-1680, 1970.

7. Stehelin, D.R., Guntaka, R.V., Varmus, H.E. and Bishop J.M., Purification of DNA complementary to nucleotide sequences required for neoplastic transformation of fibroblasts by avian sarcoma viruses. J. Mol. Biol. 101: 349-365, 1976.

8. Bittner, J.J., Some possible effects of nursing on the mammary gland tumor incidence in mice. Science, 84: 162, 1936.

9. Gross, L., "Spontaneous" Leukemia developing in C3H mice following inoculation, in infancy, with Ak leukemic extracts, or Ak embryos. Proc. Soc. Expl. Biol. and Med., 76: 27-32, 1951.

10. Poiesz, B.J., Ruscetti, F.W., Reitz, M.S., Kalyanaraman, V.S., Gallo, R.C., Isolation of a new type C retrovirus (HTLV) in primary uncultural cells of a patient with Sezary T-cell leukemia. Nature 294: 268-271, 1981.

References
(continued)

11. Brugge, J.S., Erikson, R.L., Identification of a transformation - specific antigen induced by an avian sarcoma virus. Nature 269: 268-271, 1981.

12. Huebner, R.J. and Todaro, G.J., Oncogenes of RNA Tumor Viruses as Determinants of Cancer. Proc. Natl. Acad. Sci. USA, 64: 1087-1094, 1969.

13. Stehelin, D., Varmus, H.E., Bishop, J.M., Vogt, P.K., DNA related to the transforming gene(s) of avian sarcoma viruses is present in normal avian DNA. Nature 260: 170, 1976.

14. Shih, D., Shilo, B., Goldfarb, M.D., Dannenberg, A. and Weinberg, R., Passage of Phenotypes of Chemically Transformed Cells via Transfection of DNA and Chromatin. Proc. Natl. Acad. Sci., 76: 5714-5718, 1979.

15. Slamon, D.J., de Kernion, J.B., Verman, I.M. and Cline, M.J., Expression of Cellular Oncogenes in Human Malignancies. Science 224: 256-262, 1984.

16. Dickson, C., Smith, R., Brookes, S. and Peters, G. Tumorigenesis by Mouse Mammary Tumor Virus: Proviral Activation of a Cellular Gene in the Common Integration Region int-2. Cell: 37, 529-536, 1984.

Ms. OAKAR. Thank you, Dr. Feller. You know, it's so interesting. $200 million sounds like a lot of money to all of us. But when you place that $200 million next to where we are and some of our priorities; cluster bombs cost more than $200 million. We give those to other countries. It's just so absurd in terms of where our priorities are.

And we saw in our various budgets recently, and it's not political saying this: We saw cuts in cancer research. And Senator Pepper, I want to say on behalf of my chairman, was the person who fought the hardest to restore it. And because one or two members start questioning, the one or two different researchers that perhaps didn't do the optimum job, we threw out all the good research that was done, and what you're telling this committee is that in the seventies, because of the funding that we appropriated and the President signed into law, because of that appropriation bill, we saw a breakthrough in analyzing the cells, et cetera; you're more technically aware of the names than I.

Dr. FELLER. Right.

Ms. OAKAR. And that if we continue and have an accelerated momentum, we are going to see a major breakthrough in our different approaches to curing and possibly even a cure.

Dr. FELLER. That is right.

Ms. OAKAR. But if we don't, shame on us in terms of our priorities.

Doctors, let me ask the three of you, will we ever see anything like, will I ever see anything like a vaccine for my young nieces that, are also in this hereditary bracket, and other young girls that are and the children of the patients who are here, who were here? Are we ever going to see a vaccine or something like that for—and I know what we've—what we can do now, and I'm really pleased that we can do certain things now.

But I want to talk about futuristic kinds of notions. I loved it when Kennedy said we're going to put a man on the Moon in a decade, and we did it. I guess that's where I am. Do you think we're ever going to do that?

Dr. STRAX. Well, let me give you an idea about something else. There is a program, a project, that has already been OK'd, and it's going to start July 1, supported by the National Cancer Institute. And this is directed to the problem that has been mentioned. We have to screen large numbers of women, because we don't know who is going to get a breast cancer. The genetic concept is important but 80 percent of the women with cancers we find at Guttman Institute have no high-risk factors at all. Most have had many children and many had their first child when they were young. This lady we saw here this morning, had her first child when she was 21. She has no family history but yet she had a cancer.

And most cancers that we see are in such women.

So, the concept has a reason that there must be some, true risk factor that we could detect that would tell us which woman is really at risk. And then it would make screening much easier because we could concentrate on those at risk.

The project that has been funded, involves just that. It involves what we call promoting factors. The cause of breast cancer will lie

in the domain of my colleagues. They will find the cause. They will be able to turn it off.

I haven't got that much time to waste, or to wait. And so what I would like to do is to find out what I can do to shut off a cancer that may be brewing in a woman.

Ms. OAKAR. Right.

Dr. STRAX. And this leads us to the possibility of finding the risk marker in the woman that will tell us which one is going to get a breast cancer. We know that it must be connected with the female hormones, because men very seldom get breast cancer. And that these female hormones in many women are not as nicely balanced as they should be. Most of the risk factors that we already know about are connected with disturbances of these female hormones.

This study that we are about to start involves a large number of important people at the New York University Medical Center, which is presumably running this study, men in the Imperial Cancer Research Fund in London and people in the Netherlands Cancer Institute. It will be a prospective study. A large number of women will be examined, some 40,000 women. They will have blood taken a certain way. That blood will be saved. Some of those women within the next 2 or 3 years will develop breast cancer. We think that we will be able to differentiate the kind of blood combination of these hormones in a woman who develops a breast cancer, as compared to the woman who has not developed a breast cancer.

And so if we find this probable combination, we will then have a true risk factor.

And if we can find that this combination hold up, then we can have hopes of straightening out the combination, bringing the combination back to normal and perhaps prevent the disease from developing. This study is about to start officially July first. And we hope that within five years we will have the kind of information that will be helpful to us. This does not mean that we should not be looking into the other areas that my friends have been talking about.

Ms. OAKAR. Absolutely.

I think that sounds very exciting, that finally we're going to get into studying those numbers of women, in that context.

But if I just ask the question, are we going to see a breast cancer vaccine one of these days?

Dr. FELLER. Let me comment on that. I know that you have brought that up and I know that Rose Kushner has raised that question also.

As you know, we at our laboratory at Georgetown have been looking for a human breast cancer virus for almost 20 years. I think my first research project at the NCI was to study the mouse virus, mouse breast cancer virus, and then for over 15 years we, at Georgetown, have been looking for a breast cancer virus.

It now appears that probably in the human there may be a virus but it's so closely linked to the oncogene and the switching on of the oncogene, that I really think that we have to do the oncogene research first.

I don't know, Madam Chairman, whether a vaccine is possible. It depends on whether certain kinds of viruses or specific oncogenes are associated with human breast cancer.

As Rose Kushner pointed out, research for the breast cancer virus studies was diminished, was decreased. I pointed out that Dr. Gallo, who has now come forward, with the AIDS virus, that he persisted for 20 years in looking for a similar virus in human leukemia. Many scientists discouraged him and said that he was wasting his time. But Dr. Gallo, and I think he should get a Nobel prize for persistence, if nothing else, because he persisted and he now has shown that there is a virus that probably is associated with certain forms of leukemia.

Now, if we could have had that support and that money for breast cancer, we may have uncovered a virus. I don't know.

Ms. OAKAR. Why can't we do it all? That's my question. Why do we have to have various wonderful research projects compete for the same pot of money, and they're probably all very important, even if they don't lead to a specific goal, through serendipity you find out other things, as I think you all pointed out.

Dr. Knudson, did you want to make a quick statement?

Dr. KNUDSON. I think that it would not be a good idea to place too much hope on vaccines for most cancers. People have looked very hard for these viruses and do not find them. For hepatitis and liver cancer, yes. And for some others, I think yes. But I think most of us feel that there is some fundamental change in one of our own genes that has occurred in most cancers, and there is no way of producing a vaccine against such a change.

My own interest in oncogenes, and Dr. Fellers' too, is partly related to our own knowledge of Rous sarcoma that was first described by Dr. Rous in 1911. There are such things as temperature-sensitive mutants. When you grow the virus-infected cells at one temperature, they are very malignant and will kill an animal. If you grow them at a higher temperature, the virus oncogene is inactivated and the cells revert to normal. Now, that tells us that the continued action of that oncogene is necessary for the continuing proliferation of the cancer. If the oncogene is turned off, the cancer reverts to normal. So far our chemotherapy and our radiation have been aimed at killing cancer cells; now we can dare for the first time to think of correcting cancer cells.

Ms. OAKAR. Correcting them instead of killing them. Isn't that exciting? And, of course, Rose is shaking her head thinking, no, she still wants a vaccine. I guess I do too. But I want all of it. I guess I want it all. And I don't see why, in this wonderful world of ours, with all you magnificent thinkers, we can't come up with it, as long as we give you the resources to do the job.

I wanted to close by thanking you and I want to thank all of our witnesses. I think this is the first of, hopefully, a series of hearings.

I went to the Soviet Union recently, and talked about arms control. When we met with the Women's Institute, the women, you know, and we were always debating about who was wrong and who was right about arms control. But you know what? The one thing that united all of us was the need to cure cancer, and specifically the women were very concerned about breast cancer, and all of a sudden we broke open—we started talking about that and then we led to other ideas relative to other plateaus.

I think it will be very interesting to have some of the great thinkers throughout the world come to a hearing, if we could ever

afford to do that, to meet with all of you. And I'm sure that you do do that.

But it's my hope that this hearing, which my chairman was so gracious for having and the wonderful staff we have, in preparing it, will be of some help to the people of our country for the present and for the future.

I'd like to, in particular, thank Dr. Kuller, who is on loan to the subcommittee, who did so much wonderful work in helping prepare it, in getting some of the good witnesses that we've had. I don't know if he's here yes he's—in the back of the room. And I'd like to thank Bill Halamandaris, the staff director, and Kathy Gardner, and Melanie Modlin, and my interns, Vince and Sammi, and I would like to thank the minority staff member, Mark Benedict, and the recorder, and I also want to thank Millie Vinicor on my staff who went beyond the call of duty in terms of all the things that we put her through. But among other things, her interest and involvement in the subject.

And all the women who inspired this hearing. There are a lot of women who have written to our subcommittee and to me personally and others, indicating the need for something like this and for cancer to get on the—for Congress to get on with it and start focusing on this issue, again which is so important to all of us.

I want to thank the press for being here, because without that form of communication we can't do it. A special thanks to all the witnesses and Rose Kushner for all the great information she gives me, sometimes on a daily basis, and doesn't even charge a nickel. And all the people in the audience, including my nephew, Dr. Phillip Demio, who is a recent graduate, and I know that you learned some good things from these scholars, who are your peers.

So, thank you all very much.

We're not going to say that we adjourn this meeting. We're just going to say that we're going to continue and we're going to help in your battle to get the funding you need as well.

The meeting is adjourned.

[Whereupon, at 2 o'clock p.m., June 28, 1984, the hearing was adjourned.]

APPENDIX 1

[Submitted for the record by Carolyn Alford, Midlothian, Va.]

1984 SESSION, CHAPTER 88, REENROLLED

S. 350, Approved March 8, 1984

AN ACT To amend the Code of Virginia by adding a section numbered 54-325.2:2, relating to informed consent for treatment of breast tumor

Be it enacted by the General Assembly of Virginia:

1. That the Code of Virginia is amended by adding a section numbered 54-325.2:2 as follows:

§ 54-325.2:2. Informed consent for treatment of breast tumor; paragraphs required in form.—Before a physician operates on a patient for a tumor of the breast, a consent form shall have been executed which includes the following: "CONSENT FOR TREATMENT OF BREAST TUMOR"

Sign option (a) or option (b), or option (a) and option (b).

(a) Side (right or left) Breast Biopsy.

Patient's or other authorized person's Signature

(b) If it is determined that I have a malignant tumor in my breast or other breast abnormality requiring surgery, then I authorize Dr. —— to perform such operations or procedures, including breast removal, which are deemed necessary.

Procedure: ——.

Patient's or other authorized person's Signature.

President of the Senate: ——.

Speaker of the House of Delegates: ——.

Approved: ——.

Governor.

STATE OF CALIFORNIA,
Sacramento, CA.

DEAR FRIEND: As you know, the "Breast Cancer Informed Consent Law" (SB 1893) became effective January 1, 1981. This law requires that a summary of effective alternative medically viable methods of treatment be provided by the State of California to physicians for distribution to their patients.

Finally, after two years of concerted effort on the part of concerned physicians, breast cancer patients, para-professionals and other interested persons, we have been able to produce a brochure which discusses breast cancer treatments. We hope this material will form the basis for the breast cancer patient to discuss the various alternatives with her physician, and seek other options if she so desires.

The majority of women will not develop breast cancer in their life-time. Nevertheless, it is the disease about which health-conscious women have the most anxiety; much of this anxiety and fear is based on misinformation. Applied knowledge of this disease will not only serve to reduce women's anxiety about it, but will also lead to a higher rate of cure. The idea for this legislation came from one of my constituents who contacted me regarding her deep concern for other women to be aware of all medically viable alternatives for the treatment of breast cancer.

All of us who have worked on this publication believe that any woman facing the possibility of breast cancer has the right to receive all the information available in order for her to take an informed and intelligent decision as to which procedure is best suited for her stage of the disease and the effect on the quality of her life.

We are the second state to have this law. Massachusetts was the first and Wisconsin followed us. We are the only state to have a written brochure.

I hope you will find this summary informative.

Sincerely,

DAVID ROBERTI.

Breast Cancer Treatment Summary of Alternative Effective Methods—Risks, Advantages, Disadvantages, January 1983

[This summary is required by SB 1893, "The Breast Cancer Informed Consent Law", effective January 1, 1981—Prepared by the State Department of Health Services based on recommendations of the State Cancer Advisory Council]

[Printed by Senate Reprographics, compliments of Senator David Roberti, President pro tempore, California State Senate]

Introduction

You have a treatable disease and are entitled to know about the various medically effective surgical, radiological and chemotherapeutic treatment procedures available.

This brochure has been developed to assist you to understand what these various treatment procedures are, their advantages, disadvantages, and risks.

The treatment of cancer is quite complex. It must be individualized. The choice of therapy may be difficult to make. It is important for you to have this basic information about the methods of treatment so that you may discuss them more fully with your physician as they apply to your case. This will help you understand what treatment programs may be used and what their effects may be in your individual situation. Using this information as a basis for discussion, you and your physician should be able to make an informed choice.

Because cancer is a serious disease, it may be appropriate for either you or your physician to seek additional opinions if either of you desires. Your consent is required before any treatment is carried out and you have the right to participate in making the final choice of the treatment procedure(s). Your physician has a corresponding right to withdraw from the case if he chooses.

It is very important to take a reasonable amount of time to obtain enough medical information and consultation to make a final informed decision. But prolonged delay may interfere with the success of your treatment. Making this choice is an important step. Once you and your physician have reached a decision about your treatment, you will have a positive attitude which will be a tremendous help as you and your physician begin to carry out the treatment of your cancer.

Management of Breast Cancer

Management of breast cancer is achieved by the cooperation of appropriate specialists in the field: the primary (personal) physician for general support and coordination; the surgeon for diagnosis by biopsy and specific surgical procedure for removal of the breast tumor; the pathologist for gross and microscopic diagnosis; the radiation oncologist for supervising and administering radiation treatment; the medical oncologist for specialized management of the patient's care and administration of chemotherapy. In actual practice these members proceed fairly independently but maintain liaison by telephone and written reporting.

Treatment Alternatives: Advantages, Disadvantages, Risks

If your diagnosis is breast cancer, it is important for you to understand there is enough time to make a careful decision. Prolonged delay and failure to get adequate treatment may result in the deterioration of your situation. In contrast, the benefits of modern breast cancer therapy far outweigh the risks. This is especially true when treatment is undertaken early. The risk may be small or serious, and its occurrence may vary from frequent to rare. There is a wide range of potential benefits and risks from the various treatment procedures for the different stages and kinds of breast cancer. Before deciding on your course of therapy, you should discuss with your physician the particular benefits and risks of the treatment methods suitable for your individual case.

Diagnosis

Diagnosis is the scientific determination of the nature of the lump. It is made by the pathologist who examines the tissue from the breast lump (breast biopsy) under the microscope.

The breast biopsy entails the surgical removal of part or all of the lump under suitable anesthesia. Unless the lump is quite large it is usually removed in one piece (excisional biopsy). (A large lump may be biopsied with a special needle or by surgically removing a small sample.) The tissue removed by biopsy provides materi-

al for the definitive test for cancer, namely the examination of tissue under the microscope by the pathologist. If cancerous, part of the fresh tissue may also be studied for receptors for hormones (estrogen and progesterone), which could be important if future treatment decisions become necessary. (Only about 20% of breast biopsies are cancerous; the remainder represent less serious conditions.)

The procedure for obtaining the biopsy should be discussed with you since you must make a decision between two courses of action—the One-Step or Two-Step Procedure.

In the One-Step Procedure, you and your physician decide beforehand that if the biopsy shows cancer and if surgery will be the treatment of choice, the entire procedure (biopsy, diagnosis by pathologist, and the appropriate surgery) will be completed in one operation.

In the Two-Step Procedure, the biopsy is done under local or general anesthesia and no additional operation is performed at this time. After the pathologist examines and reports on the biopsy, the surgeon reviews the pathology report with you and discusses with you the various treatment options available and effective for your particular case. A decision is then made by you and your physician on which procedure is preferred by you for your individual care.

Prior to the procedure you choose, a general medical evaluation which may include any or all of the following diagnostic procedures is usually done to determine your individual situation:

Your medical history (including family history of cancer);
Physical examination;
Blood tests evaluating function of various systems, e.g., liver, kidney, immunity, etc.;
X-ray films (chest, bones, etc.);
Breast x-ray films (mammography);
Radioisotope scan (bones, liver, brain, etc.);
Computerized tomographic body scans (specialized x-ray views of any or all internal organs and bones);
Sonograms (pictures of internal organs made with ultra-sound waves).

Treatment recommendations are individualized. They are based primarily on the extent (stage) and type of disease present as well as other factors related to your personal health.

Surgery

This process involves removal of the tumor, and either a portion of the breast, all of the breast, or all of the breast and some surrounding tissues as well.

Radical (Halsted) Mastectomy

The Radical (Halsted) Mastectomy is not commonly used today except in unusal cases. In this procedure, the entire breast, nipple, some of the overlying skin, underlying chest muscles, nearby soft tissue and lymph nodes extending into the armpit are removed.

Advantages

If cancer has not spread beyond breast or nearby tissue, it can be completely removed. Examination of lymph nodes provides information that is essential in planning future treatment.

Disadvantages

Removes entire breast and underlying chest muscles. Leaves a long scar and a hollow area where the muscles were removed. May result in swelling of the arm, some loss of muscle power in the arm, restricted shoulder motion, and some numbness and discomfort. Reconstructive (plastic) surgery and fitting of breast prosthesis are difficult.

Modified Radical Mastectomy

Entire breast, nipple, some of overlying skin, nearby soft tissue and lymph nodes in armpit are removed. Chest muscles are left intact, but overlying covering of muscle is removed.

Advantages

Retains the chest muscles and muscle strength of arm. Swelling of arm occurs less frequently and is milder than after radical. Cosmetic appearance is better than with

radical. Apparently as effective as radical, but not if cancer is large or has invaded the muscle sheath. Cosmetically effective reconstructive surgery is usually feasible.

Disadvantages

Entire breast and part of overlying skin are removed. In some cases removal of lymph nodes in armpit may be incomplete. Some persons may experience swelling of the arm.

SIMPLE MASTECTOMY

The main breast structure but not overlying skin is removed. Underlying chest muscles and often armpit lymph nodes are left in place. Many surgeons remove some of the armpit lymph nodes through a separate small incision under the arm to determine if cancer has spread to nodes. Often followed by radiation therapy.

Advantages

Chest muscles are not removed and strength of arm is not affected. Swelling of arm occurs infrequently. Reconstructive surgery is usually feasible.

Disadvantages

Breast is not preserved. If cancer has spread to armpit lymph nodes, it may remain undiscovered unless these nodes are sampled or removed at the time of surgery; adequate treatment could be delayed.

SEGMENTAL MASTECTOMY, PARTIAL MASTECTOMY AND LUMPECTOMY

If cancer is small and detected early, a segment of the breast containing the tumor is removed. Many surgeons also remove some armpit lymph nodes through a separate incision to check for possible spread of cancer. Most cancer experts feel this type of operation should be followed by radiation therapy and some feel chemotherapy should be used in selected cases as well. These procedures are relatively new and long term results are being documented.

Advantages

Most of the breast remains. Reconstructive surgery is usually easier if needed at all. Loss of muscle strength and swelling of the arm are unlikely to occur. Commonly used as first step for *Radiation Therapy as Primary Treatment in Early Breast Cancer*, especially if preservation of the breast is desired.

Disadvantages

Most cancer specialists feel these procedures may be incomplete unless armpit lymph nodes are removed for pathological examination and person is given radiation therapy or a combination of radiation therapy and chemotherapy. Otherwise, spread of cancer into armpit lymph nodes or undetected areas of cancer present elsewhere in breast may go untreated and chance for cure may be lost.

Radiation (X-Ray) Therapy

Radiation treatment of local tissues of the body, known as radiotherapy, can destroy cancer cells while producing less injury to surrounding tissues. Radiation for treatment may come from a number of devices, e.g., super voltage x-ray, linear accelerator, Betatron, Cobalt-60 and radioactive isotopes. The source and type of radiation is chosen to suit the requirements of the individual.

RADIATION THERAPY AS PRIMARY TREATMENT IN EARLY BREAST CANCER

This approach has been used for about 10 years in this country and for about 20 years in Europe for the treatment of early breast cancer. After pathologic diagnosis by biopsy and surgical removal of the local tumor, external radiation therapy is used to treat the remainder of the breast, the lymph nodes, and the chest wall. This is then followed by a radiation "boost" to the biopsy site with radioactive sources temporarily introduced into the area of the excision. Sometimes the boost may be given with more external irradiation (or electron beam).

Advantages

The breast is preserved. It may be mildly to moderately firmer. Usually there is minimal or no visible deformity of surrounding tissues. After competion of the treatment, the skin usually regains normal appearance.

In early breast cancer, lumpectomy or segmental resection, with radiation as the primary treatment, has demonstrated results that currently appear equal to long established surgical procedures.

Disadvantages

A full course of treatment requires daily outpatient visits for four to six weeks. Treatment may produce skin reaction similar to sunburn and may cause temporary difficulty in swallowing. Radiation therapy can affect bone marrow where blood cells are made. This may limit the dosage and effectiveness of later chemotherapy if it is needed. A small area of scarring, permanently visible on x-ray examination, may develop in the lung, but usually causes no symptoms.

RADIATION THERAPY AS A SUPPLEMENT (ADJUVANT) TO SURGERY

Following surgery, examination of the surgical specimen by the pathologist may show the cancer has spread outside the breast and into armpit lymph nodes or local surrounding areas. Radiation therapy will usually control cancer cells remaining in these areas. The treatment of advanced cancer often requires the consultation and coordinated efforts of the surgeon, radiation oncologist and the medical oncologist (see below).

Advantages

The goal of radiation therapy is to destroy cancer cells in tissue in the radiation treatment area which improves control of or stops the spread of cancer in the treatment area. Modern equipment gives very precise control of the x-ray treatment. Radiation therapy may be used to treat localized metastases.

Disadvantages

The major side effects are the same as those listed under radiation therapy as a primary treatment. When cancer is treated by radiation therapy as a supplement to surgery, there may be wide variations in the extent of the treatments required depending on the problem or site of disease being treated.

CHEMOTHERAPY

Medical oncologist is the specialist who usually plans and administers the chemotherapy and may coordinate the patient's management with other physicians. Chemotherapy is designed to destroy breast cancer cells that cannot be removed surgically or by radiation or their combination.

In recent years important and effective advances in breast cancer treatment have been made in this area, especially advanced cancer. Different drugs or a combination of drugs are administered orally or by injection. This program is adapted to the individual and may continue at intervals for six months to two years or longer depending on the cancer being treated and the drug program being used.

SUPPLEMENTAL (ADJUVANT) CHEMOTHERAPY

Chemotherapy supplements primary surgical or radiation treatment when it is likely the patient has a cancer which has spread into or beyond nearby lymph nodes. Such patients have a higher risk of recurrence than those whose lymph nodes are found to be free of cancer. Supplemental chemotherapy may reduce this risk considerably.

Advantages

Increases the effectiveness of surgery or radiation therapy and reduces the risk of breast cancer recurrence. Works to stop its growth at distant sites in the body.

Disadvantages

Most chemotherapy drugs have reversible side effects. Some side effects are minimal while others can cause discomfort, including nausea, temporary loss of hair, bone marrow depression (resulting in temporary susceptibility to infection and bleeding tendency), anemia, loss of appetite and fatigue, and rarely damage to heart muscles. Also may depress reproductive function and cause change of life symptoms. Newer techniques of administration and dosage reduce the side effects of chemotherapy.

CHEMOTHERAPY FOR RECURRENT BREAST CANCER

Anti-cancer durgs, taken alone or in combination with other modalities, can arrest the disease, help to relieve symptoms, and prolong the life of a patient who experiences recurrence of breast cancer.

HORMONAL THERAPY

Many breast cancers are sensitive to female hormones (estrogen and progesterone) and are partially controlled by them. In many treatment centers, fresh tissue from the tumor (specimen or biopsy) can be tested to measure this hormone sensitivity (estrogen receptor assay). In some breast cancer patients, beneficial effects can be received by adding hormones, removing glands that produce them, or by administering durgs (anti-hormones) that counteract the hormones produced by the body. Hormone therapy often increases significantly the effectiveness of other cancer therapy.

INVESTIGATIVE TREATMENTS FOR BREAST CANCER

Clinical trials are new treatments which are not yet generally available. Laboratory or other reliable studies may indicate a new cancer treatment procedure or therapy program could be better than ones in current use. Research to measure effectiveness is conducted in clinical trials by many major cancer treatment groups. The new treatment methods are put to general use only after long term evaluation by cancer experts when they find the new treatment gives results as good as, or better than, established treatments.

BREAST FORMS

Breast forms (prostheses) are made with a variety of substances such as silicone, foam rubber, silastic, viscous fluir or glycerin. Fitted individually and worn in brassiere pockets, they can give the form, weight, and appearance of a normal bustline. The right bra for you may very well be the one you've always worn. Your health insurance generally covers a portion of this cost with your physician's prescription.

RECONSTRUCTIVE BREAST PROCEDURES

Reconstructive plastic surgery may effectively restore the form of the breast and adjacent tissues lost at surgery. Implants of breast prostheses or surgical transfer of body tissues may be used. Usually at least two surgeries are required to achieve desired results, but in some cases advance planning can minimize this. The possibility of reconstructive surgery should be discussed with your physician in advance of a definite surgical treatment procedure. You should investigate the extent of financial coverage available through your health insurance for this procedure.

FOLLOWUP

The success of cancer treatment depends not only on early detection and effective treatment, but also on a careful, consistent follow-up program to detect cancer recurrence as early as possible if it should occur. Consistent regular visits to the treating physician and monthly self-examination are essential. New methods of detection and treatment are being continually developed and can be used to your advantage.

Many very helpful and thoughtful women who have been through a similar experience can lend you their support and guidance. They can be contacted through your physician, your hospital, your local unit of the American Cancer Society, or the National Cancer Institute's Cancer Information Service.

SUMMARY

This brochure is intended to make you aware of the effective alternative methods of treating breast cancer available in California, and your role in choosing the method to be used in your care. In order to reach a decision on the treatment method, it is important for you to understand the nature of the disease, the extent of your problem, the treatment needed, the method or methods of providing that treatment suitable to your particular situation, and finally the results that may reasonably be expected.

This is best done by having a complete evaluation followed by a thorough discussion with your physician(s). The brochure should assist you to participate in these discussions by providing essential background information so you can ask questions you need answered, and help you to understand what your physician is talking

about and how the choice of cancer treatment method will affect you and your circumstances.

Many important details are necessarily left out and you should look to your physician for your complete and current information. Being well informed and having thoroughly discussed the alternatives will make it easier to make a knowledgeable decision about your course of treatment. It will give you justified confidence you have made the best choice possible. This will be a tremendous help to you and your physician as you carry out your treatment and establish your follow-up program.

HEALTH AND SAFETY CODE, SECTION 1704.5

California Physicians and Surgeons are required by law to inform patients of alternative effective methods of treatment for breast cancer. This brochure describes medically viable treatment including surgical, radiological (x-ray) chemotherapeutic (drugs) treatments or combinations thereof. It has been printed in a form which may be reproduced by physicians for distribution to their patients. If physicians wish to obtain printed copies they may be purchased from:

State of California, Publications Section, P.O. Box 1015, North Highlands, CA 95660

The cost of the brochure:

25 copies	$3.40
50 copies	6.15
100 copies	9.15

JULIET RISTOM, CALIFORNIA

By the time Juliet Ristom of Los Angeles learned that her breast lump was suspected to be cancerous, her doctor had already reserved an operating room for a mastectomy. When she asked about alternatives, he refused to give her any information. After 11 days of research on breast cancer, she chose to have a lumpectomy followed by radiation therapy. Throughout her search, she was frustrated and infuriated by doctors' reluctance to discuss treatment options. When her treatment was completed, she contacted her state senator, David Roberti, urging legislation requiring physicians to provide breast-cancer patients full information on their treatment options. In 1980, Senator Roberti introduced "The Breast Cancer Informed Consent Law", and Ms. Ristom became a one-woman lobby for breast-cancer patients' rights. With little support from women's groups in the state, she was successful in getting the legislation passed over opposition of numerous medical groups.

The bill required that breast-cancer patients receive written information on treatment alternatives. The California Cancer Advisory Board was given the task of preparing a suitable document. The task took two years and several dozen drafts because of disagreements on emphasis and wording. Senator Roberti insisted that Ms. Ristom be allowed to comment on the brochure, and she was adamant that it not place excessive emphasis on mastectomies as opposed to other types of treatment.

The brochure became available in March, 1983. In her lonely battle for breast-cancer patients, Juliet Ristom estimated she lost $75,000 in business from her personnel agency by spending so much time on her crusade. She has no doubt, however, that she made the right decision. Freedom of choice was the issue at stake.

Copies of the State of California's brochure "Breast Cancer Treatment/Summary of Alternative Effective Methods/Risks, Advantages, Disadvantages," are available through the American Institute for Cancer Research. For your copy of this informative brochure, check box 2 on the "Free Information Request" card, or write to AICR national headquarters.

[redacted] SOUTH OGDEN DR.,
Los Angeles, CA, August 12, 1980.

To each Assembly member:

DEAR——— ———. I am attaching the statement I made at the hearing of the Senate Committee on Business & Professions Code, as well as a rebuttal to the letter sent by the CMA to State Senator David A. Roberti, dated July 2, 1980, for your information and study.

Senate Bill 1893 will not help me because I took control of my treatment and will always do so. However, I have worked very hard for its passage in order that breast cancer victims will be aware of *all* procedures and not be forced, through ignorance, to accept a mastectomy if it is at all possible to avoid it. If after learning of the various procedures, a patient chooses a mastectomy—that's fine. It is that patient's choice, and he or she will live comfortably with it.

The United States is a country with vast resources, and monies labeled for cancer research. Yet the medical profession as a whole is not abreast of the various modalities of treatment that are available. Every man, woman and child in the world should have the right to the best and most complete medical information available in order to save their lives. The horror is that far too often, as I might have done, they will fall into the hands of a doctor using therapy which is already obsolete.

An honorable physician is one who values opinions other than his or her own. The patient's welfare, not his or her personal vindication, is their prime concern. If all members of the medical profession practiced as the Hippocratic Oath, to which they swear, directs, there would be no need to legislate them—nor would there be the incredible number of malpractice suits against them. We are aware that physicians are not infallible, but neglect, lack of sensitivity and compassion, a desire to play God, is unforgivable and a crime against Man.

Please vote for the passage of Senate Bill 1893.

Sincerely.

REBUTTAL OF POINTS RAISED BY THE CALIFORNIA MEDICAL ASSOCIATION IN THEIR LETTER TO SENATOR DAVID ROBERTI, DATED JULY 2, 1980

1. ". . . legislation . . . may interfere with sound medical treatment . . ." it encourages and creates sound medical treatment.

2. ". . . this lack of knowledge is a failing of our public education system . . . a shortcoming of efforts toward public health information" "public ignorance concerning disease and treatment . . . is a societal problem . . . . not a medical problem which can or should be dealt with in the context of the individual patient's relationship with a physician who is doing the best he or she can to effect a cure of a tragic and emotionally traumatic disease."

The community should play an active role in prevention not in diagnosis and/or in recommending treatment.

Physicians are paid by their patients to inform them. This responsibility should not be shifted to public health departments. A physician is not doing his best when he or she withholds information as to alternative treatments or procedures from the patient, regardless of the disease.

3. "Cancer of the breast is often an emotionally devastating affliction." It is always an emotionally devasting affliction.

4. . . . "Each educational measures should reach the patient before she is confronted with a diagnosis of actual or possible malignancy. . . ."

This is really ludicrous. No woman is going to make a study of breast cancer, because none of us feel we are ever going to get it. This disease is so frightening that we avoid reading anything about it.

According to the CMA, every person should take up the study of medicine because we are all subject to getting any of the diseases known to man. None of us can be certain we are only going to get one disease in our lifetime.

5. "The relationship between a physician and a seriously ill patient is one requiring sensitivity on the part of the physician, a delicate probing and investigation of the total needs of the patient, and a careful formulation of a medically sound treatment plan that includes informing the patient of the nature of her illness and the risks as well as benefits of proposed treatments and procedures."

How I wish this were true. Unfortunately, it is not. My case and hundreds of thousands of others—including those women who have contacted me directly for counseling—were subjected to the rigid and closed minds of our physicians. These breast surgeons look at breasts, not the woman. They don't care what the mutiliation of woman's body does to the quality of her life. Comments like, "What does a 60 year old women need with breasts", or, (to a woman in her forties) "You're past the child-bearing age, so losing your breast shouldn't be important to you."

6. "No printed pamphlet, directed to the public generally, can replace or even meaningfully supplement the physician's thorough explanation to the individual patient of her breast cancer and the proposed treatment thereof in a manner that meets the unique needs of that patient."

I have already described the lack of information given the patient, and the CMA has already stated in their letter that they do not believe the physician should have to educate the patient; and I have already commented on the lack of sensitivity and compassion that exists with the physican.

Insofar as the pamphlet is concerned, I would have given anything in the world to have had such a pamphlet at the time I was diagnosed as having breast cancer. It would have given me a sense of direction, even if my surgeon refused to give me the names of doctors who specialize in various alternative procedures. And it would

have spared me eleven days of deep depression and terror. Instead I had to go on my search blindly. By an accident I would get one name; by a coincidence I would get another; or one contact would lead me to another, and so on. I had to rush through reading as much material as possible because my surgeon did not feel it was important to tell me what stage of the disease I had (which happens to be extremely important in order to make a decision as to the most effective procedure). In fact, when I asked him if he would do staging tests prior to a mastectomy, he told me he would not. Yet, if the cancer had metastasized in another part of my body, it would have been useless to perform a mastectomy. Also, with such a pamphlet guiding me, I probably could have made up my mind in at the very least half the time it took me. It is possible that my taking 11 days to make by decision could affect my health.

7. "We suspect that the need for SB 1893 perceived by its proponents is based on medical practice as it existed in past years when radical mastectomy was the only proven effective procedure to halt breast cancer. Recent advances in radiation therapy and chemotherapy have made the mastectomy less of a preferred procedure, however, and as a serious surgical procedure with severe emotional and psychological ramifications it is recommended only after a careful evaulation of the patient's individual medical needs has ruled out less invasive alternatives."

Wrong. We are talking about all forms of mastectomy (radical, modified radical, and simple) versus alternative procedures.

You will be interested to know that even though the National Institute of Health at a conference in June 1979 stated, "The Halsted radical mastectomy initially introduced for locally advanced breast cancer has been the traditional treatment for the past 80 years. Selection in the past appears to have been based on this tradition rather than tailored to a patient's stage of disease or histologic type." , a recent survey by a Ph.d in Public Health at USC showed that 25% of the mastectomies being done today are the Halsted radical. Statistics after statistics have been proven that the modified or simple mastectomy has far better survival rates than the radical. And, for your information, statistics so far have proven that alternative procedures have survival rates as good, if not better in many instances, than mastectomies.

I am delighted that the CMA is aware of the recent advances in radiation therapy and chemotherapy. It's tragic that most of them do not share information about these "advances" with their patients.

APPEARANCE OF JULIET R. RISTOM BEFORE THE SENATE COMMITTEE ON BUSINESS AND PROFESSIONS CODE HEARING RE SENATE BILL 1893 ON APRIL 9, 1980

LADIES AND GENTLEMEN: It is most appropriate that this hearing on legislation requiring that all breast cancer victims be told of alternative procedures is being held at this time because April is "Cancer Month"—and so all cancer victims are made even more aware of the possibility of their life span being shortened as a result of having had this tragic disease.

I was diagnosed as having breast cancer last July. My surgeon—considered one of the very best in Los Angeles—did not think it was important to come to the hospital to give me this tragic information and to describe and consult with me on the surgical procedure he wanted to perform and its possible after effects. Instead, he phoned me at 5:15 p.m. while I was all alone in my room; gave me the results of the biopsy; and that he had the operating room reserved for the next morning to perform a modified radical mastectomy. Even though I was in a state of shock, I had the presence of mind to tell him to cancel the operating room: that I wanted out of the hospital as I wanted to search alternative procedures. His comment was "what alternative procedures"—and I told him that one of them was radioactive implants. He never told me that right in that hospital was the top man for this particular procedure. To digress for a moment, I told the surgeon I wanted the specimen sent to Sloan-Kettering in New York for a second opinion. Their recommendation was a simple mastectomy rather than the crippling modified radical my surgeon wanted to do.

I will not go into the 11 days of hell I went through interviewing surgeons, radiologists, members of the staff at USC Cancer Information Center pathologists, and the Reading of three of the best books on breast cancer so that I could make an intelligent decision—one that would not destroy the quality of my life, which I felt sure the mutiliation of my body would. I chose radioactive implants and this procedure was done by Dr. Ronald W. Thompson at Cedars-Sinai where the biopsy had been preformed.

I was told I should be brief so I will end this opening statement with a quote from a letter I wrote to my gynecologist who told me that regrettably he could only help me if something was wrong with me from the waist down, but he wanted to know which procedure I chose. When I called him and told him, he told me he was glad because if it was a member of his family he would have searched for alternative procedures—yet he had sent me to a breast surgeon who only did modified radical mastectomies.

"When a women is examined by you or your associates, you examine her breasts for lumps. If she has a lump, of if she calls you, as I did, and says she has a discharge of blood from her nipple, you recommend a breast surgeon. The surgeon recommends a biopsy, and, if it is malignant, he recommends that a mastectomy be performed immediately—either a radical (which, tragically, is still being done), or a modified radical (many times only moderately improved over the radical). Both of which are nothing more than the mutiliation of the woman. She is always told that time is of the essence, and at her emotionally weakest moment and within the psychological pressure of a hospital environment, she agrees to the mastectomy which has to alter the quality of her life to a devastating degree. She doesn't have the time, or the knowledge, to look for alternative procedures. For example, who does lumpectomies? Certainly a preferable choice than having her breast completely cut off. To whom can she look to tell her about alternative procedures? Certainly not to the surgeon who only knows one procedure and has his mind closed to any others. And the surgeon is essentially a stranger to her.

"I feel that all doctors who take on the responsibility of examining a woman's breasts, be they gynecologists or internists, must reevaluate this responsibility. You are the doctors who have to know about the alternative procedures and have at hand the names of doctors you can refer a woman to. She is most familiar with the doctor she sees on a consistent basis: that doctor should be a part of her medical team; she should be able to look for help from that quarter.

"I am not advocating radioactive implants per se. What I am advocating—and am fighting for—it freedom of choice. A woman has the right to decide what she wants done to her body, but if she doesn't know she has choices, how can she choose?"

One out of 11 women will get breast cancer—50 percent of them will die from it. Everyone of you will be touched by it, either through a relative or a friend.

[Three other women then made a statement endorsing the bill; one from the National Council of Catholic Women, the National Council of Jewish Women, and the Nurses' Organization, all from the Sacramento area. After they were finished, I took the microphone again and made this statement:]

"I would like to add that I am just as whole and normal as I ever was."

[From the Los Angeles Herald Examiner, Thursday, Sept. 18, 1980]

How One Woman Changed the Law on the Treatment of Breast Cancer

(By Joan Zyda)

A year ago, Juliet Ristom's surgeon phoned her in her hospital room in Cedars-Sinai Medical Center in Los Angeles and gave her the dreaded news: There was a cancerous lump in her right breast and it would have to be removed.

As shock and fear overcame her, the surgeon told her, rather clinically, "I have the operating room on reserve for you tomorrow morning . . ."

"I asked about alternatives," Ristom said, "and his answer is seared in my brain: 'What alternatives?' he snapped.

"I said, 'Cancel the operating room! I want out of this hospital! I'm going to search for options and make my own choice,'" she said.

The surgeon thought she was crazy, and warned her that time was critical, she said, but Ristom, a Beverly Hills businesswoman who described her age as "mature," was undeterred. "In a manner of speaking, I took control of my own treatment."

For the next 11 days, she raided local libraries for books, magazines and scientific studies, phoned the USC Cancer "hot line," and interviewed several psychologists, doctors, radiologists and pathologists about breast cancer, the leading cause of cancer deaths among women.

Through her efforts, Ristom discovered several treatment options for her type of breast cancer, such as radioactive implants which would leave her breast intact; a "lumpectomy"—surgical removal of the lump only; radiation therapy; or a combination of treatments.

She chose radiation implants, a complicated procedure involving the insertion of small nylon tubes into the breast in a geometric pattern that are then loaded with radioactive sources.

Moreover, she had the relatively painless two-month procedure performed by another physician at Cedars-Sinai: Dr. Ronald W. Thompson, the head of the radiology department.

The successful treatment "kept me whole as the day God made me," Ristom said, adding, "The only marks I have are the faded marks of the needles."

Ristom's cancer story might have ended there. But she became convinced through her own investigation that doctors were not informing breast cancer patients of medically accepted options and instead expected them to submissively undergo disfiguring radical mastectomies that might be unnecessary.

"Doctors ignore the alternative procedures and frighten women into having their breasts chopped off at their weakest moment—when they're waiting in the hospital," she said. "To summarily mutilate a woman's body, without taking her into the decision-making process, is a crime."

Inspired by the Massachusetts Legislature's recent adoption of a sweeping patients' rights bill, Ristom, who is single and childless, became a one-woman lobbyist for the rights of breast cancer victims.

About two weeks after she was discharged from the hospital, Ristom said she wrote a memo about her experience and sent it to her state senator, David Roberti, D-Los Angeles. She also met with the lawmaker and explained her situation.

"He took me absolutely seriously, and was as confounded as I was over the outrageous medical procedures concerning breast cancer victims," Ristom said.

Roberti introduced legislation, signed into law yesterday by Gov. Edmund G. Brown, Jr., that requires physicians and surgeons to make the time and effort to inform breast cancer patients about medically approved alternatives.

The law, an amendment to the physicians-and-surgeons portion of the state's Business and Professions Code, also states that doctors must inform patients of those alternatives "by means of a standardized written summary to be developed by the Cancer Advisory Council in layman's language and in a language understood by the patient."

Failure to comply with the code means a doctor or surgeon "may be disciplined" for "unprofessional conduct," the law states.

Opposition to the law was strong from California medical associations, which have traditionally fought any government meddling in their profession.

But Thompson, Ristom's second doctor, contends that while he doesn't like to "see medicine legislated," the law "doesn't create an intolerable burden on doctors and women have the absolute right to know the options."

Thompson said members of the mostly male medical profession have shown a tendency to deal with women's problems as simply as possible, without always keeping an eye on their patient's overall well-being.

He claimed that many of his patients for radioactive implants, an accepted alternative for some since the 1960's, have had to "hustle as many as six, seven, eight doctors before they get to my door."

"Many surgeons think it's easier for them to just remove the breast," the doctor said. "If cancer of the penis were as widespread as breast cancer, you can be sure there would be an alternative to removing it."

[From Time magazine, Nov. 1983]

Easing Women's Constant Fear

Breast-cancer patients can face a future without disfigurement

(By Claudia Wallis as reported by Mary Carpenter (Venice) and Carol Foote (Santa Cruz))

At some point in her life, one out of eleven American women will be told she has breast cancer. The dread of this moment is perhaps the single biggest fear that women have about their health. For Nina Miller, 42, of Santa Cruz, Calif., it happened two years ago. Her reaction was typical. "Total hysteria. My only thought was, they're going to multilate my body, and then I'm going to die." But Miller has

---

Note.—This will not be true in Georgia unless the legislature will pass a law protecting a woman's right to control her body.

lost neither her life nor her breast. Like a small but growing number of breast-cancer patients in the U.S. she avoided a mastectomy and instead was treated with a simple removal of the breast lump (lumpectomy) followed by radiation therapy.

Until recently, such breast-sparing techniques were universally considered to be inadequate and dangerous. Today, the evidence is to the contrary. Last month, at a meeting at the National Cancer Institute in Bethesda, Md., noted Italian Oncologist Umberto Veronesi presented the results of a landmark ten-year study comparing survival after a mastectomy with survival following a less disfiguring operation called quadrectomy. His conclusion: "There is absolutely no difference."

Veronesi, who heads Milan's respected National Cancer Institute, bases his conclusion on the treatment and follow-up of 700 Italian patients. Half were treated with a mastectomy and half with a quadrectomy, plus radiation if the malignancy extended to lymph nodes under the arm. All of the women in the study had a very early stage of breast cancer, with tumors measuring less than three-quarters of an inch in diameter. A decade after treatment, 96% of the women in both groups were alive and apparently healthy. Significantly, the study defied the longstanding dictum that anything short of a mastectomy increases the risk that cancer will recur. In fact, the incidence of tumor recurrence was the same in both groups, less than 5%. Said Dr. Bernard Fisher, chief breast cancer surgeon at the University of Pittsburgh. "This makes it awfully hard to justify the radical mastectomy.

Fisher is one of a small number of American medical dissidents who have long opposed the indiscriminate use of mastectomies for breast-cancer patients. At a recent conference in Venice, Italy, sponsored by Bristol-Myers, he and a number of other U.S. doctors reported on their successes with more limited treatment. According to Dr. Samuel Hellman, physician in chief of New York's Memorial Sloan-Kettering Cancer Center even patients with tumors as large as two-inches in diameter may require nothing more than a lumpectomy followed by radiation. Though this approach involves removing even less tissue than Veronesi's method does, the results with some 350 patients seem to be just as good. Moreover, Hellman notes, the physical appearance of the treated breast is "good to excellent" in four out of five patients.

Despite the persuasive force of these studies, Hellman admits, "the consensus among U.S. physicians is still in favor of mastectomy." Indeed, his own institution, Sloan-Kettering, has long been a bastion of radical surgery. A survey conducted in 1980-81 by the National Cancer Institute found that 80% of breast cancer patients in Atlanta and Detroit were being treated with a modified radical mastectomy, an operation in which the breast and some chest muscle are removed. Up to 5% were still being treated with the old-style radical mastectomy, in which so much pectoral muscle is removed that arm motion may be limited for life. Only 7% of patients in Atlanta and 10.8% in Detroit had received a lumpectomy, a quadrectomy, or some other form of breast-sparing surgery.

Many physicians have resisted the new techniques because they fear that without mastectomy cancer will be more likely to recur and more patients will die. The ten-year Italian results may convert the skeptics although Veronesi warns. "Next the surgeons are going to want to see the 15-year outcome and then the 20."

Because the mastectomy is so firmly entrenched in American medicine, many breast-cancer patients are never told about the alternatives. To remedy this California, Massachusetts, Minnesota, Hawaii and Wisconsin have passed laws that specifically require doctors to inform patients of options in treatment before a final decision is made. Even so, reports Hellman, the various approaches are generally offered with "varying degrees of enthusiasm, depending on the physician."

The best candidates for a lumpectomy are women with small tumors that have not yet spread. Most doctors also prescribe additional treatment, with radiation as a precaution against tumor recurrence. For women with a small degree of spreading (measured by counting the number of malignant lymph nodes), radiation treatment is strongly recommended. Women with more extensive spreading may also be candidates for a lumpectomy, but for these patients chemotherapy might be used as an added safeguard. According to Veronesi's colleague, Dr. Gianni Bonadonna, a leading authority on chemotherapy, there is really only one reason for a complete mastectomy: when the tumor is so large that it fills one-third or more of the breast. In that case, he asks, "What would you be leaving behind?"

The key to getting by with less surgery, and improving the chances for survival, is early detection of the disease eight out of ten women treated for the incipient stage of breast cancer, known as stage 1, survive for ten years or more, the percentages drop off sharply with later detection.

Because the risk of breast malignancy increases with age, the American Cancer Society has for nearly a decade urged women 50 and over to have their breasts X-

rayed annually. This summer, the A.C.S. revised its recommendation to include women age 40 through 49, citing the improved accuracy and safety of low-dose mammography. The first line of defense for women of all ages, however, is self-examination. In 1970 only 25% of breast tumors were detected at stage 1. By 1980, as more women learned how to examine their breasts, the proportion had grown to 60%.

Despite the success rates for early detection of tumors, many women are so terrified by the prospect of a mastectomy that they delay treatment. As former Patient Judy Feinman, 46, puts it: "I knew there was something wrong, but I just didn't want to face it." Perhaps says Bonadonna, the availability of less disfiguring treatments will lead to less procrastination. "Women will realize that if they come in early, they will not be punished by the removal of a breast."

GEORGIA WOMEN'S COALITION FOR MEDICAL FREEDOM, INC.,
College Park, GA, January 2, 1984.

DEAR ELECTED STATE OFFICIAL,
State Capitol, Atlanta, GA.

Time Magazine (see reverse side) reported the facts as released by National Cancer Institute; we strongly protest this being allowed to continue in GA. In 1973 the U.S. Supreme Court ruled that the woman's right to control her body was a civil right under the 14th Amendment. We want that right spelled out in law in Georgia and implemented in the case of breast cancer patients through a preprinted form furnishing adequate data on alternatives and risks, for us to make our own decision concerning lumps in the breast. A copy of California's pre-printed form has been furnished to our sponsor and is attached for your review.

Women are asking "are our doctors incompetent; do they need remedical training to update skill and knowledge? Is forced mastectomies a potential fraud on patient, insurance and government funds? Or, is this a possible form of male brutality-surgical rape of defenseless uninformed females? What ever the reason, it must be stopped through protective laws.

Current research findings confirm the effectiveness of breast sparing surgery as stated approximately 15 years ago by Dr. Geo Crile (Cleveland Clinic) and of Dr. Oliver Cope (Harvard) and more recently by Dr. Barnard Fisher, Chief of Breast Surgery Research, Univ. of Pittsburgh.

Equally important is the warning given by Ms. Alice Hamm (NCI) who stated "beware of benign diseases that MIMIC CANCER". "Do not accept as gospel one doctor's opinion or decision based on frozen tissue slide. Insist on proof of cancer through Permanent Tissue Biopsy" . . . something rarely done in Georgia. She only confirms statements in "Breast Diseases" (doctor text book) by Haagensen who reported (as did N.E. Journal of Medicine) untold number of women needlessly subjected to disfiguring mastectomies when no cancer existed.

Note: Dr. Stephen Gallager, Prof of Pathology, M.D. Anderson Research Center states "There is no evidence to show a delay of even 5-7 days waiting for a confirmation or patient decision, makes any difference in patient survival".

It is time to initiate human rights in medical care in Georgia and reduce malpractice suits due to damaged angered persons who were not adequately informed to make an intelligent decision.

MARIE STEINMEYER, *Director.*

[From the San Juan Star, Tuesday, Feb 21, 1984]

VICTIM CALLS MASTECTOMY A "HUMAN ISSUE"

(By LEON DANIEL)

RICHMOND, VA. (UPI)—Carolyn Alford, mother of four, sat in the living room of her suburban home and asked if I would like to see where her left breast had been.

"Would you be embarrassed?" she inquired.

Over the next two hours it became clear my momentary discomfiture was nothing compared to the real physical and mental anguish Mrs. Alford suffers daily.

Still fresh-faced at 40, she is a pretty woman with the soft drawl of her native Virginia.

Gravely, she removed her wine-colored knit vest and then a cameo at the collar of her frilled white blouse.

She unfastened several buttons, loosened the pink strap of her brassiere and exposed a patch of flesh where her breast had been.

The creamy, fine-textured skin on the left side of her chest was as flat as her hopes had been on a morning nine years ago when she awakened in a hospital with the certain knowledge an important part of here was irrevocably lost.

At 31, just after the birth of her last child and only son, her surgeon had assured her he would remove from her breast only what he called "a harmless little lump."

After four hours of survey, she awakened with excruciating pain in the recovery room to discover she had undergone a radical Halstead mastectomy.

Mrs. Alford soon was to learn that meant she had lost forever not only a breast but much of her chest wall, her left pectoral muscle and the lymph nodes from her armpit.

"The pain was like I had been scalded," she recalled.

If she did not know then the full extent of her loss, no one had to tell her her breast was gone.

"I just knew it," she said. "The pain was so intense."

She also came to know that, while she was unconscious on the operating table, her husband had given the surgeon permission to perform the mastectomy.

Mrs. Alford acknowledged frankly her marriage had been strained by the impossible decision her husband was forced to make on the spur of a nightmarish moment.

"He started drinking heavily after the operation," she said.

Carolyn Alford is among a growing number of women in the United States who demand legislation outlawing performance of a biopsy and mastectomy during the same operation with a signed "informed consent" in advance giving the surgeon permission.

She said her husband, who for years had refused to discuss with her the operation and its painful physical and mental effects, has undergone treatment for alcoholism and now supports her lobbying efforts.

"Mastectomy is not a feminist issue," she said quietly. "It's a human issue."

If you doubt that, observe the hurt in a brave woman's eyes as she shows you the patch of flesh where her left breast once was.

In a statement he prepared for Virginia lawmakers, Richard Alford said the surgeon who operated on his wife had "demanded the biggest decision of my life from me in just a few seconds."

While waiting in the hospital lobby for his wife to undergo what both had been assured was a minor surgical procedure, Alford was summoned to the reception desk where the receptionist handed him a phone, saying, "Use this one."

"I was literally on my toes, leaning across the desk, visitors on either side of me asking for room numbers," Alford recalled.

"The doctor said, 'I'm sorry, Mr. Alford, but the tumor is malignant. I need your permission to perform surgery.' "

Stunned, Alford asked, "What choice do I have?"

A successful salesman for a high-technology manufacturer, Alford recalls the surgeon saying, "I can return her to her room," but also stating, "We don't have much time to wait."

"What do I do?" Alford asked the surgeon. He said the surgeon replied, "Come to the bottom of the steps and someone will bring the forms for you to sign."

To his everlasting regret, Alford signed them.

Breast cancer is the No. 1 cancer killer of women in the United States. Until just a few years ago, the radical mastectomy was the standard treatment.

Most women are now advised to choose a less traumatic procedure called a simple mastectomy, in which only breast tissue is removed and underlying muscles and lymph nodes are left intact.

Also available is the lumpectomy, in which only diseased tissue is removed. Doctors disagree whether this procedure is effective.

Carolyn Alford, at age 31, with her life and its future quality at stake, was not given any options.

No one asked her if they could remove her breast. No one told her they were going to do something that would rob her of sexual self-esteem.

Mrs. Alford was not even told such actions were essential to save her life, a proposition that would seem to have been at least arguable then.

On Thanksgiving Day, 1974, life seemed full of promise to Carolyn Alford as she and her mother chatted while washing the dishes after a festive family dinner.

"Mother was saying she had read you could detect breast lumps by examining yourself," she recalled. Later, after a shower, she told her mother, "I think I've found a lump."

The surgeon her obstretician recommended confirmed her finding and scheduled an operation to remove the lump.

"He never said anything about a mastectomy," said Mrs. Alford, who added that she and her husband were assured the small tumor almost certainly was benign.

Mrs. Alford was unable to ask the most important question of her life until the answer was academic. She put that question, not to her doctor, but to her husband, who was standing beside her in the recovery room when she awoke in intense pain.

"Richard, I have cancer, don't I?" she asked.

Her next question, put silently to herself, was, "Am I going to live?"

"The first things I thought about were my four children and death," she said.

In the years that followed, however, Mrs. Alford's thoughts, fed by the physical pain and mental anguish she suffers daily, ranged widely, perhaps wildly.

"I think I'll go to my grave wondering if I really had cancer," she said.

She said the first six months were the most difficult because of the physical pain of the operation that left her scarred from armpit to waist.

"I had a baby and I couldn't even change his diapers," she said. "My mother had to give me baths."

She said her despair was compounded by her husband's refusal to discuss the operation.

"Once I said to him that what happened to me was not fair and he just said that life is unfair," she recalled. "I cried a lot. He knew I resented his signing the forms. I really didn't want him to take the blame but I wanted him to know I didn't like what had happened to me."

Despite strains on the marriage, Mrs. Alford sought counseling and tried to lead a normal suburban life. Her bridge partners did not even know she had had a mastectomy.

She said that by the time her husband was getting treatment for alcoholism, "I had so much anger I didn't know how to deal with it."

About a year ago Mrs. Alford read a newspaper story that changed her life.

It stated that an all-male panel of Virginia state senators had voted 8-6 to kill a bill requiring doctors to obtain informed consent from patients facing breast surgery for cancer.

At last, it seemed, she had found the proper target for her anger.

She was incensed that these men seemed to take the position they knew what was best for women and their bodies.

"Nobody can know what it's like unless they carry around a body like mine," she said.

After reading that newspaper account, Mrs. Alford walked across the road and, for the first time, unburdened herself to a neighbor, telling her of her mastectomy.

"I loved it when she listened and seemed to understand" Mrs. Alford said.

She then channeled her anger into lobbying to revive the dead legislation, working with feminists but insisting she was not one herself. A similar bill now is considered to have a good chance to pass.

"When I started I thought ERA was a detergent," she joked.

Mrs. Alford has a cause now but the pain, physical and mental, never leaves her for long.

"It hurts when my daughters try on swim suits or tennis clothes," she said. "I can't wear those things."

During a family vacation at the beach, she said, she spent most of her time inside.

And then there are jokes, told innocently, that hurt her deeply.

"Do you know how many jokes there are about boobs?" she asked, plaintively.

There also remains some real bitterness.

When the 260 stitches were removed from her body, she recalled, the surgeon surveyed his work and commented, "It's beautiful."

"What I know now is that surgeons love to cut," she said.

At times over the years she did not understand her own feelings about what had happened to her.

"I kept feeling guilty for not being appreciative for living," she said. "People would tell me I should just be glad to be alive."

Mrs. Alford is angered by physicians' groups that oppose the legislation she believes in so strongly.

"Why are they so determined that we not have a choice about what happens to our bodies?" she asked.

The Medical Society of Virginia, according to its spokesman, has said the society approves of a consent form in principle but does not want it mandated by law.

Some doctors fear such legislation would open the floodgates for interference in the treatment of other diseases. Some contend it would encourage women to delay needed surgery and thus undergo anesthesia a second time, which in itself is a risk.

Carolyn Alford, who had never before been an activist, has found the strength to stand up in public and look doctors and lawmakers in the eye when she says, "I don't think because you're put to sleep you should lose control of your body."

To make men understand what she is talking about, she also can muster the courage to bare with dignity the patch of flesh where her left breast once was.

[From the Wall Street Journal, Wednesday, June 13, 1984]

Medical Debate—Controversy Intensifies Over the Best Method To Treat Breast Cancer

An Experiment Is Measuring Results of Mastectomies, Preservation Treatments

(By Jerry E. Bishop)

Weighing Recurrence Risks

New York—Any woman with breast cancer who walks into Manhattan's big Memorial Sloan-Kettering Cancer Center can expect to receive the best treatment medical science has to offer. But the best science has to offer may well be determined by which door of the sprawling center she enters.

If she walks in the York Avenue entrance to see Samuel Hellman she will learn there is an alternative to mastectomy, or removal of the breast, provided the tumor is still small. That alternative is lumpectomy, or surgical removal of the tumor, followed by a course of intense radiation treatments. There are still some long-term uncertainties about this new method, Dr. Hellman will carefully emphasize. But experience so far indicates it is just as effective as mastectomy in curing early-stage breast cancer—and it preserves the breast.

But if the woman were to walk into the offices of Jerome Urban two blocks to the west on 68th Street she will get a different picture. The breast-preservation treatment is available, Dr. Urban will tell her, "but I can't recommend it." The uncertainties about the new technique are still too great to take a chance, Dr. Urban will explain. The mastectomy, on the other hand, is a proven cure for breast cancer.

Drs. Hellman and Urban represent, in a single institution, two sharply opposing points of view in the long-running controversy over the treatment of early breast cancer. (A third view is that of those favoring a lumpectomy *without* radiation). The controversy has been going on with varying degrees of intensity for almost two decades and has led to sharp and emotionally charged confrontations among cancer specialists. It has evoked accusations by militant feminists that the male-dominated medical profession has been callously and unnecessarily mutilating women. And it has created an anguishing decision process for thousands of women who discover suspicious lumps in their breasts.

Major Experiment

Now, the controversy is about to flare anew.

In the next few weeks, researchers plan to publish their first report on a major experiment that was undertaken to settle the controversy. The experiment was launched in 1976 and involves hundreds of breast-cancer patients from 28 medical centers; the women, who volunteered to participate, were assigned randomly by a computer to one of three courses of treatment: mastectomy, lumpectomy or lumpectomy followed by radiation. By comparing the fates of the women over the years, the researchers hope to determine whether the breast-preservation therapies are as effective as the tried and true mastectomy.

It is far too soon for the experiment to have produced any meaningful results. Researchers generally regard the five-year point, dating from the beginning of treatment, as the first critical benchmark in measuring the treatment's efficacy, and the last woman to volunteer for the experiment did so only this past January. And while there are preliminary results, they are being kept under a tight lid of secrecy—to the point that the researchers even refuse to reveal the number of women participating in the experiment.

The scientists fear that fragmentary leaks and stories in the lay press on such an emotionally charged issue are likely to create new confusion between doctors and their breast-cancer patients. Even after the report is published in a medical journal, new debate is expected to ensure as the various sides cull data to buttress their cases.

About 115,000 women develop breast cancer each year, making it the most common form of female cancer. In about 40% of these women, the cancer is discov-

ered after it has begun to spread from the breast into the neighboring lymph glands. There is almost universal agreement among doctors that for these women the mastectomy, often followed by chemotherapy or radiation, offers the best chance of arresting the malignancy.

Key Question

The controversy, instead, focuses on the 60% of women who discover the breast tumor when it is still small and confined to the breast. Decades of experience show that a woman undergoing a mastectomy for early breast cancer has an 85% to 90% chance of being alive five years later and a good 75% to 80% chance of being alive 10 years later.

Nevertheless, a small but increasing number of these women will seek treatments that promise to preserve the breast. Some will seek out surgeons who believe that lumpectomies alone will suffice if the cancer is caught early enough. Others will go to a handful of medical centers offering lumpectomies followed by radiation therapy for early breast cancer. For all these women bent on breast preservation, the key question is whether these treatments are as effective as the mastectomy in getting rid of hidden clusters of cancer cells that might become another life-threatening tumor years later.

Nowhere, perhaps, are the issues of mastectomy versus breast-preservation therapy more clearly drawn than here at Memorial Sloan-Kettering.

The 50-year-old Dr. Hellman is a radiation therapist who uses X-rays and gamma rays to treat disease, particularly cancer. In the 1960s when he was at Yale University's medical center in New Haven, Conn., Dr. Hellman was involved in treating Hodgkin's disease with radiation. "Some surgeons began sending over women with advanced breast cancer who had refused mastectomy to see if we might be able to do something for them," he recalls.

Unacceptable Damage

Radiation therapy for breast cancer had been tried unsuccessfully years before. At that time, however, the X-rays were too weak to penetrate very deep into the breast; to deliver a cancer-killing dose of X-rays to a tumor meant causing unacceptable amounts of damage to the overlying healthy tissue.

But by the mid-1960s, radiation therapists such as Dr. Hellman were beginning to use deep-penetrating "megavoltage" X-rays that could reach a tumor without causing undue damage to healthy tissue. There was some hope it might be helpful in women with breast cancer.

Dr Hellman subsequently met the late Martin Levene, a radiation therapist at Harvard. Dr. Levene also was interested in radiation therapy of breast cancer, and the two men began exploring this new mode of treatment for breast cancer at Harvard's Joint Center for Radiation Therapy in Boston.

At first, most of the women patients were referred to the center because their breast cancer was too advanced to be operable. But about a third of the first 100 patients were women with early-stage breast cancer who adamantly refused to have a mastectomy. Today, the center treats about 200 women a year with radiation, a large portion of whom have early breast cancer, says Dr. Hellman, who moved to Memorial Sloan-Kettering a year ago as physician-in-chief but retains his ties with the Boston center.

At the radiation center on Binney Street in Boston, the procedure varies in detail from patient to patient. But, generally, if the pathologist who examines the excised tumor gives the go-ahead, the first move is to temporarily implant tiny pellets of radioactive iridium in the breast. Ten days to two weeks later, the patient begins a series of daily treatments of the megavoltage X-rays. Between the radiation from the pellets, which are removed after a few days, and the external X-rays, the total radiation dose over the weeks should reach cancer-killing levels.

The odds are high that the breast will emerge unscathed other than the small biopsy scar. In at least 73% of the cases at the Boston center, both the woman and her doctor agree the radiation left no noticeable permanent effects on the breast. The remaining patients did experience some noticeable reddening and scarring but only 4% of all the patients classified cosmetic results as "poor."

But does the treatment cure the cancer? In the first 10 years, beginning in 1968, the center treated 357 women for early breast cancer. So far, only 18 have had a recurrence of breast cancer. But Dr. Hellman and others caution that so few women have passed the critical five and 10-year marks, the statisticians can't yet get a firm measure of the treatment's long-term effectiveness.

Still, borrowing a statistical technique that life-insurance actuaries use to predict life expectancies of various groups, the center's statisticians calculate that a woman treated with the radiation therapy has a 96% probability of being alive and well

five years hence if her tumor was caught when it was small and localized. If the tumor is larger and one or two lymph nodes have hints of cancer, there is still an 87% probability she will be alive and free of cancer five years following radiation therapy.

These probabilities indicate that survival rates are just as good as those achieved by mastectomy, Dr. Hellman and colleagues say. In fact, in their formal report, the researchers state flatly that radiation therapy "is applicable for the large majority of patients having breast cancer."

"I Could Be Wrong"

Dr. Hellman concedes that "I could be wrong," that as the years pass the survival rates may change for the worse—or the better. Then there is the question of the 18 women who had recurrences of their breast cancer. They all underwent mastectomy for the recurrence but the surgery cured only half of them. "We don't know whether these women would have been better off if they had had a mastectomy in the first place," Dr. Hellman explains.

If women knew they could save their breast if they had a suspicious lump checked out immediately, more breast cancers might be caught in their earliest, most curable stages, Dr. Hellman argues. "A number of women who've come in first noticed a lump in their breast six, 12 or even 18 months earlier but had delayed seeing a doctor because they feared they would lose their breast," he explains.

Thus, breast-preservation therapy, its adherents believe, offers the first chance in 30 to 40 years to lower the death rate from breast cancer. This death rate has remained stubbornly unchanged since the 1950s at about 23 deaths per year for every 100,000 women in the population.

But two blocks away, in his private office, Dr. Urban has a different perspective. Drs. Urban and Hellman agree that the entire breast, not just the lump, has to be treated in breast cancer. "I think I can do a better job surgically and Sam Hellman thinks he can do just as good with radiation," Dr. Urban says.

Probabilities vs. Experience

Dr. Urban challenges the statistics indicating radiation therapy is as effective as mastectomy. For one thing, he says, the radiation therapists carefully select patients who are most likely to benefit from radiation. While there is nothing wrong with this, in and of itself, the results can't be be compared directly with those of mastectomy which include women who would be poor risks for radiation therapy. Such comparisons of dissimilar groups of patients, Dr. Urban says, may make radiation therapy look better than it really is.

But it is the use of actuarial probabilities in place of actual experience that Dr. Urban finds most upsetting. Dr. Urban performed mastectomies on 544 patients before 1971 and the actual results are known—97% of those with localized tumors and 88% of those with cancer that had spread slightly were alive and free of cancer 10 years later.

The more critical statistic, Dr. Urban says, is the number of these 544 women who had a recurrence of their breast cancer in the 10 years after their treatment. This tells how effective the treatment was in getting rid of the hidden cancer cells. Among Dr. Urban's mastectomy patients, only 6% have had a recurrence within 10 years after treatment.

Published reports from France as well as the U.S. indicate a recurrence rate of 15% to 18% among women treated with radiation 10 or more years ago, two to three times as high as among women undergoing mastectomy, Dr. Urban says. (Dr. Hellman and other radiation therapists reply that the statistics include many patients who were treated before the most effective radiation techniques had been worked out.)

While Dr. Urban tells his patients the breast-preservation treatment is available, he nonetheless believes that saving the breast isn't worth this extra risk of a recurrence. "The breast is of secondary interest; it's the life of the patient that's primary," he says.

"I tell them there's a good chance they can have a breast reconstruction later if they want and if necessary I'll even show them pictures of how good the reconstruction can be," he says. Actually, he says, only about 5% of women who have mastectomies chose to have a breast reconstruction later.

Women who have had mastectomies are more resilient than most people think, Dr. Urban says. He points to a psychological study published last year of 20 women who had mastectomies and 18 women who had the radiation therapy. The women with mastectomies had more negative feelings about seeing themselves nude. Other-

wise, there was very little difference between the two groups in feelings of sadness, guilt, anxiety or other symptoms of psychological distress.

DOCTORS MUST TELL PATIENTS THEIR OPTIONS

(By Joe Manning)

New state rules require physicians to tell patients about "alternate modes of treatment," or face the possibility of disciplinary action by the Medical Examining Board.

"It's safe to say that the vast majority of physicians don't know about these new rules," a spokesman for the Medical Society of Milwaukee County said.

The rules, which have been in effect since Oct. 1, require physicians to note on patients' medical record that the patient have been "communicated to" about "alternate viable modes of treatment."

"The communication shall include the nature of the recommended treatment, alternate viable treatments, and risks or complications of the proposed treatment, sufficient to allow the patient to make a prudent decision," said the rules.

Wisconsin is the only state to have a law requiring physicians to discuss alternative treatments for all ailments, said Deanna Zychowski, spokesman for the Medical Examining Board.

"It's meant to be all-inclusive," said State Rep. Betty Jo Nelsen (R-Shorewood), who sponsored the bill. Nelson said she introduced the bill after one of her constituents was told she had cancer and needed a mastectomy, but was not told of other treatments.

The 38-year-old woman did not want a mastectomy. After spending three months in Boston, Mass., receiving radiation treatment, she learned that the same treatment was available in Milwaukee—she just had not been told of it by her doctor Nelsen said.

Nelsen's bill was unanimously passed by the Legislature in the spring of 1982.

Zychowski said the law allows any patient to complain about a physician who fails to inform the patient about alternative treatments.

"Now, physicians have to document that they discussed alternatives with their patients," she said.

Zychowski said complaints will be investigated and, if warranted, physicians will be warned "the first time." The Medical Examining Board can suspend the licenses of physicians who fail to comply with the rules, she said.

She warned that physicians found in violation of the rules would be dealt with firmly. "The Legislature was very serious about this," she said.

Paul E. Hankwitz, a Milwaukee physician, said most physicians tell patients about the different treatment methods as a matter of good practice.

He finds fault in the record keeping that will be required. "So much of a physician's time is taken up with documenting this. There is not enough time for patients now," he said.

He said, however, that the new rules would serve health care consumers in cases where physicians did not completely inform patients.

Chesley P. Erwin, president of the State Medical Society of Wisconsin, said the new rules might go beyond the current level of medical science.

"It's not clear cut. How can we discuss alternative treatments to such diseases as AIDS (acquired immune deficiency syndrome) when there aren't any? You can't always give clear-cut answers. Some doctors look at this as interference," he said.

Donald Lord, legislative coordinator for the State Medical Society, said before the new rules became effective, physicians were legally required to tell patients what options existed and what the risks were.

"The rules will do an important thing in that it will educate those physicians who do not do this (inform patients)," he said.

Physicians are not required to explain alternatives in emergencies, or "if the communication would unduly confuse or frighten a patient or if a patient refuses to receive the communication."

The rules also read: "A physician is not required to communicate any mode of treatment which is not viable or which is experimental."

Viable is defined in the law as "modes of treatment generally considered by the medical profession to be within the scope of current, acceptable standards of care."

"The requirement is to make sure patients get all the information. All the law says is that doctors must tell patients all the choices. It's really just a standard of good practice," Nelsen said.

KEEPING AN EYE ON DOCTORS

(By Neal R. Peirce)

WEST PALM BEACH, FL—The hospital wouldn't let Alma Rose check out until she paid every cent of her bill that insurance didn't cover. But neither would the hospital authorities produce an itemized bill. Mrs. Rose refused to pay. Only when her husband threatened to call a federal marshall—noting it's against the law to hold a person for ransom—did the hospital relent.

That incident, says Mrs. Rose, "is one of a lifelong series" of negative experiences which has made her into a rebel against the American medical establishment. Now she is a local leader in West Palm Beach, a city with many senior citizens and one of the country's highest doctor-to-population ratios, to bring doctors and hospitals to heel.

In January the year-old "People's Medical Society," claiming 35,000 members nationally and growing by 1,000 a week, picked West Palm Beach for an intensive trial run of the physician-account-ability campaign it hopes may soon sweep the country.

All of Palm Beach's doctors were asked to sign a consumer-oriented, 10-point "code of practice." Will they post fees for appointments and tests? Will they assure their patients of up-front, frank discussions of the costs, physical pain and risks of any proposed treatment? Will they describe their qualifications for the particular treatments proposed?

People's Medical Society executive director Charles Inlander says the code simply affirms basic patient rights: "No more patronizing attitudes, technical jargon, over-treatment or disregard for costs. We're only asking doctors the same they ask their Mercedes dealer's service department—up-front costs, prognosis, and 'You can't go ahead and do anything until I give you my full approval.' They only difference is we're not asking for the parts back."

By mid-February, only 47 of Palm Beach's 1,200 physicians had agreed to sign the code. And that despite PMS's month-long local campaign including sophisticated newspaper ads, television spots, public hearings and two-hour radio programs each of the five Sundays in January.

Physician indifference isn't likely to daunt People's Medical Society leaders, including founder Robert Rodale, publisher of the 2.5 million-circulation Prevention magazine. Inflated doctor bills and lab fees, questionable surgery and hospital price-gouging occur often enough to create a fertile field for consumer-based rebellion.

PMS' next project could lead to a nationwide consumer rating of doctors. PMS members are being asked to fill out an evaluation each time they visit a physician: How long did you wait? Did the doctor spend enough time with you? Did he or she discuss alternatives to proposed tests, medication or treatment? Were you told about fees in advance? On a scale running from excellent to completely unsatisfactory, how would you rate this physician?

The evaluation forms will be sent to PMS headquarters in Emmaus, Pa., and fed into computers which will maintain reports on each doctor. It's not hard to discern the potential for an immense, consumer-oriented data base, the results available either to PMS members or the physicians themselves.

The question arises—why subject the American medical establishment, perhaps including one's family doctor, to what seem such tough scrutiny?

The first answer is the roaring inflation in health costs. PMS claims physicians' average incomes, almost $100,000 a year at latest count, have risen—even after full accounting for inflation—by 3.7 times in 50 years.

Mr. Inlander acknowledges that American medicine has a remarkable record of achievement—in ever-more-sophisticated technology, in developing miracle drugs that have practically stamped out such diseases as tuberculosis, diptheria, typhoid and smallpox.

But today, he argues, chronic disorders that can't be treated with some magic pill are up to 80 percent of all disease. Life-style changes (such as more exercise, better nutrition and vitamins) are often more effective than the medications and intrusive procedures stressed in medical schools. According to an Office of Technology Assessment estimate, only 10 to 20 percent of the techniques doctors use are empirically proven.

Indeed, PMS charges, one-fifth of hospital patients end up with "iatrogenesis," doctor-caused disease resulting from unjustified surgery, adverse reaction to drugs, or overuse of antibiotics leading to the development of resistant strains of bacteria.

Alternative approaches—self-care, non-physician health care practitioners, and mutual-aid groups such as Emphysema Anonymous and Mended Hearts—often outperform physicians in support, nurturing and emphasis on prevention.

What the health-care field needs, goes the PMS argument, is a strong injection of competition, bringing to doctoring the same jolt delivered to AT&T through divestiture and the airlines and truckers through deregulation.

Outside of "doctor mystique," PMS sees a big part of the problem in medical monopoly—state medical-licensing laws that forbid anyone without a medical license from offering health-care counsel or treatment. Competitors such as acupuncturists, midwives and feminist health-care centers are often hauled into court. Organized medicine's anticompetitiveness may well intensify with the oversupply of doctors being churned out of medical schools.

PMS would break the monopoly position of the country's 450,000 physicians by dramatic changes in state-licensing laws. One approach would be to broaden the definition of "the practice of medicine" so broadly that alternative providers—from holistic health specialists to nurse practitioners—be permitted to practice, and even certify their members. State licensing could be limited, or abolished.

As medical-licensing acts come up for review under many states' "sunset laws," PMS members will be urged to seek reforms, says Mr. Inlander. He believes the states should experiment broadly. The idea would be to "let in" as many alternative practitioners as possible, "and at the same time protect the public from quacks and charlatans—whether they're MDs or others."

Alma Rose has another way of putting it: "Everybody knows the medical community has to change—doctors, hospitals, the whole profession. We need government controls, but only so much. Instead, I think the consumer route—the codes of practices, the physician evaluation forms—are the way to go."

Treatment Dilemma—Opinions Differ on New Therapy

(By Dan Patrinos)

As one controversy in the treatment of breast cancer is being settled, another, more fierce, is taking its place.

And women are finding themselves in the middle, having to consider their own needs and physicians' differing judgments.

At issue in the current debate is whether breast-saving surgery combined with radiation is as effective as a mastectomy—the removal of the breast and other tissue.

For nearly a century, and until only several years ago, the conventional approach to breast cancer was a standard radical mastectomy—the amputation of the entire breast, the lymph nodes in the armpit and the two layers of chest muscles underlying the breast.

Then came a modified version that spares the major chest muscles, but still removes the breast and the lymph nodes.

Studies involving thousands of women showed a radical or a modified surgery made no difference in survival. The type of surgery, however, did make a difference in the quality of life. The radical operation often resulted in swelling of the arm, discomfort in the chest wall and limitation of motion of the shoulder.

There is now a trend toward even more conservative surgery coupled with radiation for women whose cancers are very small when diagnosed.

This surgery may range from a so-called lumpectomy—the removal of just the tumor—to a removal of the quarter of the breast that harbors the tumor, plus lymph nodes in the armpit.

[redacted]rong evidence is accumulating that disease-free survival with lump surgery plus [redacted]ation over several weeks is equivalent to that obtained with a radical or a modified mastectomy.

"Radiation is not applicable for everyone," said James Cox, a Medical College of Wisconsin radiotherapist who practices at Milwaukee County General Hospital. "Properly selected patients do very well, and we have every indication that they will do as well as women who have their breast removed.

"The esthetic results of radiation are considered excellent. I think all patients with T1 and T2 lesions (cancers that are about 2 inches or less in size) can be treated in this way."

A Milwaukee surgeon, while conceding the equivalent survival results of the surgery-radiation approach, said a mastectomy was quick and effective.

"From my point of view, surgery can do as well as radiology in curing a patient with early stages of cancer. I can do in less than two hours in surgery and six to seven days in the hospital what would take a radiotherapist five to six weeks to accomplish," said John Hurly, a widely known surgeon at Good Samaritan Medical Center.

"For some women, a breast is more important than for others," he said. "It depends on their age, lifestyle and emotional overlay. If there is an emotional overlay, they deserve to talk to a radiologist. There are some women who feel strongly about physical appearance."

RADIOTHERAPY INCREASING HERE

J. Frank Wilson, associate professor of radiation therapy at the Medical College, said that women who have detected their breast cancer in early stages were likely candidates for lumpectomy-and radiation.

"By combining limited surgery, where only the lump is removed, with radiation therapy, we can offer women the opportunity to avoid major cosmetic, functional and psychological problems," Wilson said.

What is most encouraging about this technique, he said, "is that it may allow more women to come forward earlier to seek therapy when they know that there are non-mutilating alternatives."

Radiation therapy consists of external radiation of the entire breast and area lymph nodes. This is sometimes preceded or followed by implanting radioactive wires in the breast for a few days. The patient may also be given anti-cancer drugs.

Cox said complications of radiation therapy were few, but may include some lung inflamation and reddening and thickening of breast tissue. Fracturing of ribs happens rarely, he said.

"For the most part, women in Milwaukee are having mastectomies, although the number of surgeons in the community referring patients for radiotherapy is increasing," Cox said.

Some women fear radiation therapy and choose surgery instead, he said.

William Donegan, a Medical College professor of surgery who practices at County General, acknowledged that the early survival results of mastectomy and lumpectomy-radiation were equivalent.

"Generally, we know that results we can expect from surgery," Donegan said. "We know what happens at five years, at 10 years . . . and even at 30 years (of survival) with surgical treatment. The information from radiotherapy is still limited."

He said radiotherapists were "highly selective" in the patients they chose to treat. Results from these patients may be statistically biased in favor of radiotherapy, he said.

"I'm not saying there is a deliberate bias, but there is a potential bias in those results. And that's why one has to continue to look toward controlled trials to tell us if radiation in unselected cases—in other words, randomized series—will produce results that are comparable to those of surgery."

He noted that the National Cancer Institute in 1979 endorsed the modified radical mastectomy as the primary treatment for breast cancer.

"With radiation we know that we can't promise the woman that she is going to keep her breast, even though the radiation approach is used."

Donegan said radiation could produce undesirable results.

"The immediate complications," he said, "have included rib fractures, temporary cough, damage to the liver and damage to the heart, sometimes requiring opening the envelope of the heart to let out fluids . . . And we haven't been able to observe people with it (radiation treatment) long enough to know whether there is an increased risk of cancer due to the radiation itself."

He said a women should know the pros and cons of various treatments "so that she can make a decision that we would be willing to deliver and that she could live with after she gets the treatement.

"This is a field in transition. There's a lot of turmoil. And I feel that at this point one could possibly say safely that no one has all the right answers."

[From the Richmond News Leader, Wednesday, June 1, 1983]

Breast Reconstruction Now Offers Alternative for Many Women

(By Dawn Chase)

Seen in a plastic surgeon's album, the picutre is chilling.

Seen in a mirror, it can be devastating.

One side of the woman's naked torso is normal. Skin stretches smoothly and a breast swells or sags as God and gravity have made it.

On the other side, the breast is gone. In its place is bare flesh, sometimes pulled taut over a sunken chest and marred by a long scar.

The woman's intellect—and her doctor—tell her she is lucky to be alive and free of cancer. But the woman's lifelong vision of femininity has been molded by the bouncing breasts of Playboy centerfolds, the bountiful madonnas of art, the feeling of her own body filling out a seam dart in a tailored suit and the private enjoyment of her nipples' sensitivity.

Her scarred chest cannot compete with this vision. She is an amputee. She grieves, "one hour or one day, or one year or a lifetime," a plastic surgeon said.

The fear of this amputation is so great that, according to one physician, some women refuse to check themselves for breast lumps. They are terrified that they will find one.

That fear is realistic, according to the American Cancer Society.

The American woman stands a 1-in-11 chance of getting breast cancer. If she detects it early, she probably will survive. But she also probably will have a mastectomy, or breast-removal operation. And she almost certainly will mourn the lost breast.

Many women now have an alternative to spending a lifetime as an amputee: breast reconstruction by a plastic surgeon.

Five years ago, only about 5 percent of mastectomy patients sought restorative surgery. Surgeons had only two ways to do it and the results often were crude.

Now, however, 30 percent of mastectomy patients have breasts refashioned from their own tissues. Surgeons have at least four methods to choose from and the results often are amazingly good.

Dr. Michael Scheflan, for example, has an album of optimistic "before-and-after" pictures. Until last winter, Dr. Scheflan specialized in the "tummy-tuck" method of breast restoration at Medical College of Virginia and Richmond Memorial hospitals. He has returned to his native Israel, but the surgery continues in Richmond.

His pictures show the transition from scarred amputee to a matched set of restored breasts. In some cases, a scar continues to cut across the top of the new breasts. In others, marks of surgery are hidden under arms or breast folds, and visible skin stretches flawlessly.

Dr. John B. McCraw, a plastic surgeon who practices in Norfolk, has a set of less idealistic pictures as well. "I show those pictures to women and I say, 'Here's the deal: Sometimes it ends up this way no matter how hard we try.' "

"The main purpose is to help women dress better," Dr. McCraw said.

Not every mastectomy patient qualifies for restoration. Some have too much damage, or radiation therapy has slowed their ability to heal, or the cancer is not gone.

And not every restorative procedure can be used by every woman. The choice depends upon how much muscle she has left, how badly scarred she is, the way her frame is built and her general physical condition.

With those cavets in mind, the physicians described the restoration procedures:

Silicone prosthesis implant

In this procedure, the implant is inserted under the skin fat and chest muscle (if any muscle is left). Usually, the incision is made at the old mastectomy scar.

The surgery takes one hour. The patient spends a day or two in the hospital. Recovery time is seven to 10 days.

Women who have plenty of soft, unscarred tissue—preferably with muscles still intact—are best suited for this surgery, Dr. Scheflan said. If a woman has bad scars or skin stretched tightly, she probably would not be a good candidate, he said.

Most bodies accept silicone with little reaction. But sometimes, the body recognizes the material as foreign and forms scar tissue around it. "When it gets firm, it just looks like a struck-on grapefruit," Dr. McCraw said.

For that reason, this method is rarely used nowadays.

Breast constructed from upper abdominal tissue

In this procedure, the surgeon slides abdominal skin upward to stretch it over a silicone prosthesis and form a breast. Then he pulls up the remaining abdominal skin and fastens it under the new breast.

The scar usually is under the breast fold, out of sight on larger-breasted women. Because the chest skin is stretched, any scar across the breast probably will fade with time, Dr. Scheflan said.

The surgery takes up to two hours. The patient spends three to four days in the hospital and usually recovers within 10 days.

Women who have too little tissue to accommodate a simple silicone implant might qualify for this procedure. But tall, slender women with long torsos are bad candidates, as are women with skin so tight that it cannot be pulled up, or patients who have had heavy exposure to radiation.

Breast built of skin from the back

Called "latissimus dorsi myocutaneous flap reconstruction" in medical terms, this relatively new operation cuts tissue, complete with muscle, nerves and blood supply, from the back on the same side as the lost breast. The tissue is swung around on a pivot point, stretched over a silicone prosthesis and attached to the front. The back skin is drawn together and stitched.

The back has enough muscles to compensate for the ones that are moved to the front, Dr. Scheflan said.

The surgery leaves a single long scar on the back and an elliptically shaped scar that looks like patchwork across the breast.

The operation takes 3½ hours, with a five-day hospital stay and up to four weeks for a recovery period.

This procedures is particularly good for women who have had a lot of breast tissue removed in their mastectomy. However, if the mastectomy damaged the nerves and blood supply in the back, the woman should not have this surgery, Dr. Scheflan said.

"The big difference is that you can build in immediate droop," resulting in a more naturally shaped breast, Dr. McCraw said. For that reason, the back-flap is the most popular reconstruction method today.

The main drawback to this option is that back skin usually has a different color and texture than breast skin, so that the new breast might be a different color than the other one.

Tummy-tuck breast restoration

The medical name for this is "rectus abdominis reconstruction." In it, the surgeon cuts an elliptical section out of the abdomen, then "tunnels" it up under the skin to the chest, where he forms it into a breast.

Usually, no silicone implant is needed and the new breast has built-in muscles, fat, nerves and blood vessels.

The surgeon then pulls the upper part of the abdominal wound down and stitches it. Ideally, the abdominal scar is across the bikini line, but Dr. McCraw said it tends to be higher.

A teardrop-shaped scar surrounds the new breast, with the point of the teardrop being at the original mastectomy scar, patients report.

Like the back-flap version, this procedure is good for women who have lost a lot of skin and underlying muscle.

The surgery takes about 3½ hours. The patient spends about a week in the hospital and recovery takes four weeks.

In some women who have had this procedure, the loss of abdominal muscles makes them more susceptible to hernias. Dr. Scheflan has reported success with eliminating that problem, however.

With all skin-flap procedures, one danger is that the blood supply to the new breast will be inadequate and the tissue will die.

As he talks about his work, Dr. Scheflan gestures like a sculptor. Unlike many other types of medical specialists, he has the satisfaction of immediate results.

His patients usually walk away with their shoulders back, cancerless and shapely again, he said.

But not always.

Once, he was approached by a woman whose mastectomy had done no good. Her cancer had spread. She was dying.

"I'm well aware of my prognosis," she told him. "Regardless of how long I have to live, I want to live it as I used to be."

She asked him to do the surgery.

He did.

Mastectomy Remains Most Common Procedure

(By Dawn Chase)

Breast cancer kills more women than any other single form of malignancy.

This year in Virginia, 750 woman will die of it, according to the American Cancer Society. In the United States, 37,200 women will die. And 114,000 new cases of the disease will be diagnosed.

If the malignancy is caught early, the woman has an 87 percent chance of surviving for five years. But she probably will lose at least part of her breast.

Despite advances in radiation and chemotherapy, mastectomy still is the most commonly used way to eliminate the cancer. Most doctors contend it is the fastest and surest, as well.

Not only cancer victims have mastectomies. Women with fibrocystic disease—a tendency toward lumpy, sore breasts that carries with it a greater risk of cancer—sometimes have their breasts removed rather than go through the recurring fear that they have cancer.

Others who have one cancerous breast removed will go ahead and have the other noncancerous one removed at the same time. The American Cancer Society condones these "preventative mastectomies" only if the women has a risk of breast cancer.

Some general surgeons now are removing breasts in a way that will make it easier for the women to have reconstruction later.

To Dr. John B. McCraw, a Norfolk plastic surgeon, the ideal mastectomy scar is up and down and hidden, usually under the arm. The more muscle, skin and fatty tissue left, the easier it is to sculpt a breast. "You want a teardrop shape with a little droop," but droop depends on how much tissue is available, Dr. McCraw said.

The amount of tissue removed by the surgeon depends upon how far advanced the cancer is, said Marianne Currie, public information officer for the Virginia Division of the American Cancer Society.

Ms. Currie outlined the surgical options that breast-cancer victims have:

Radical mastectomy

This used to be the breast cancer operation, but it is rarely performed now. In it, the surgeon removes the breast, the pectoral muscles underneath it, the lymph nodes under the arm and surrounding fat and skin.

Modified radical mastectomy

This is the most frequently performed mastectomy today. The surgeon removes the breast, some lymph nodes under the arm and some chest muscle.

Total or simple mastectomy

The breast and, sometimes, lymph nodes close to the breast are removed. Radiation or chemotherapy usually follows this procedure.

Segmental or partial mastectomy

The tumor is cut out of the breast, along with a wedge of breast tissue, skin and pectoral muscle. Radiation therapy may follow this.

Lumpectomy or tylectomy

In this, just the tumor and sometimes, a bit of surrounding tissue are cut out of the breast. Radiation therapy usually follows this.

Ideally, the woman with a breast lump should know all of her options for treatment and reconstruction before she goes in for a biopsy, Ms. Currie said. But women should remember that "a lot of physicians aren't well-informed" about restorative surgery.

"If they think things are moving too quickly, where they feel uncomfortable with the procedure or the diagnosis, they should seek a second opinion," she said.

Mastectomies and reconstructive surgery can be performed at the same time. But physicians and the cancer society advise women to wait two months or so between the procedures. By then, the swelling will have subsided, the breasts will be easier to match and the woman is more likely to be satisfied with the results. Also, the woman will have a better idea of which restorative technique would be best for her.

Usually, touch-up surgery is required after the restoration. During the touch-up, the plastic surgeon does what he needs to to make the breasts match. He also makes

a nipple by drawing up the skin to form the point and grafting skin taken from the inner thigh to form the aureole.

A final postscript of reassurance. If a woman finds a lump in her breast, she should not panic. In 80 percent of cases, the lumps are benign.

NEW BREAST MAY COUNTERACT SENSE OF LOSS, ANGER

(By Dawn Chase)

Vain. Sissy. Ungrateful.

Those were some of the names that doctors called the women who demanded—and got—breast restoration surgery after mastectomies.

In some cases, the doctors sincerely worried that the newly sculpted breasts might hide recurrence of the cancer that originally threatened the women.

(Statistics have shown that there probably is no such danger, plastic surgeons say, but cancer specialists prefer a delay of two cancer-free years between mastectomy and reconstruction.)

Some doctors were under the impression that reconstructive results were so poor that they would only mutilate the women further. (That was often true years ago, but the surgery now produces reliably good results.)

In other cases, however, the doctors were reflecting personal biases. That plastic surgery is something the rich indulge in when they have nothing else to do. That one is nobler for trudging through life lopsided. That breasts have little to do with sexuality or femininity.

Small wonder that women raged. Some of them even got the feeling that their mastectomy had been unnecessary. A woman grieving over a lost breast often may imagine that the breast actually was healthy, but the surgeon liked to carve women up.

"The horrible thought has crossed my mind: I wonder if my breast *was* malignant. You know?" said one Richmond woman, whose breast was diagnosed as cancerous and removed seven years ago. Last year, she had restoration surgery.

The idea that breasts are expendable parts of the female anatomy leaves some women speechless. But not all.

"The most immediate example that comes to mind is that mastectomy means to a woman what emasculation would mean to a man," said a Northern Neck woman. She's the one whose general surgeon told her "That's for sissies," when she asked him about reconstruction many years ago.

Life without a breast, for her, was a miserable experience. "The physical sense that I was aware of when I woke in the morning was a sense of amputation," she said.

Like many women with mastectomies, she wore a breast-shaped silicone prosthesis in her brassiere. The prosthesis was fitted to match the size and weight of her other breast, but it bothered her nonetheless.

"It's an annoyance," she said. "It's one more thing that you have to do each day . . . It's not satisfactory. When you bend over, it falls away from you."

But, more, the prosthesis was a humiliation. This woman, proper and precise in her language, fell apart as she recalled one particular incident.

She was at the beach and was wearing her prosthesis under her bathing suit. "I lost the damned thing in the waves," she said. While she waited and children played in the water around her, "My husband went up and down the beach, trying to find (it)."

Finally, embarrassed, she pulled herself out of the water and set out for a replacement. She found it in the Yellow Pages, under "Artificial Breasts." "Which is a real killer," she said. "You feel like you're part of a substratum of society somehow."

"I guess, because most surgeons are men, they don't appreciate the complexity of the deformity," said Dr. Michael Scheflan, a plastic surgeon who practiced in Richmond until recently, when he moved to Israel.

Women tell themselves. "I'm not whole. I'm not as good as I used to be." And they ask, "How could he love me in the same way?"

Dr. Eloise C. Haun, A Woodstock psychiatrist, wrote about it in Virginia Medical journals.

"The breast is not just any organ. Flemish painters shed light on the breast. Chiseling Greek sculptors had a way with breasts. One is scarcely romantic about the stomach. Security is not found close to mother's kidney. Few songs attempt to lyricize the liver . . .

"The loss of a breast can mean death by suicide or a living death to the patient . . . The breast is not just any organ. It is invested with a multitude of emotions, a formidable proportion of which is anger."

Things are changing for the better . . .

Women have more and better methods of surgical reconstruction to choose from. Most major health insurers now foot the bill because they consider reconstruction a part of the treatment for breast cancer. Some general surgeons now consult with plastic surgeons before performing a mastectomy.

Women who have had the surgery are downright evangelical about it.

"They're all that way," reports Dr. John B. McCraw, a Norfolk plastic surgeon. "That's really unusual for the kind of work we do. They go out and recruit other women."

The women confirm what Dr McCraw said is the purpose of the surgery: "To dress normally . . . in a sundress or bathing suit if they choose; to counteract a certain sense of lost femininity; to be rid of an external prosthesis; and to 'forget,' in a sense, the cancer and get on with living."

From the time she awoke in the recovery room and heard her surgeon say, "You have a beautiful new breast," the Northern Neck woman said she felt, "Well, absolutely wonderful . . . I can't say that I had any negative reaction at all."

Dr McCraw said that reaction is typical if the woman has a waiting period between mastectomy and reconstruction.

"Every time I say that, there are 10 women in the audience who stand up and throw eggs and stuff," he said.

"Patients generally don't appreciate the difficulty of producing a good surgical result if it is done at the time of mastectomy," Dr. McCraw and a colleague, Dr. Charles E. Horton, wrote in Virginia Medical journal.

"This observation may be related to poor psychological preparation, too much happening at one time, never seeing the mastectomy deformity, never experiencing the mastectomy 'grief reaction' or comparing the reconstruction to the normal breast."

In other words, said Emily Parker, coordinator of the cancer society's "Reach to Recovery" mastectomy program in Virginia, "It's sort of important for the woman to have the experience of not having the breast there . . .

"Her goals have to be realistic. She has to realize that it's not going to be a natural breast."

Mrs. Parker is not one of the angry ones. She survived breast cancer 20 years ago, when the prognosis was much less hopeful, and she is very satisfied with the reconstruction surgery she has recently, even though "I'm 65 years old, and now I've got the breasts of a 16-year-old."

"The results that can be obtained nowadays are so good" but they have drawbacks, she said.

Breasts reconstructed over a silicone implant will be firmer than natural breasts. Scars may show and remain angry-looking for a lifetime. While some women report that sensation returns to the transplanted tissue, others get used to numbness. Lost muscle power may never return. Sometimes, the blood supply to the newly grafted tissue is inadequate, and the tissue dies.

And some women, having survived cancer, just do not want reconstruction. "They don't want to go through more surgery," Mrs. Parker said because it's not a simple little procedure.

"I would do it again for myself, but we are not out to sell reconstruction. The reconstruction is not a simple thing at all."

POSTMASTECTOMY PROGRAM OFFERS HOPE TO VICTIMS

(By Nan Robertson)

TEANECK, N.J. – At first, the new women come in slightly hunched over, one arm held against their side as if they were protecting something. They have had one of the most devastating kinds of surgery a woman can have—a mastectomy, the removal of a breast. The aftershock is emotional as well as physical.

"I felt injured; I felt afraid," Judy Nelson said. "I had very few expectations for this program. I had nothing but scorn for what the community of women could do. An erotic organ had been removed. It wasn't just decorative—I nursed two children with it."

Along with nearly 200 other women, Mrs. Nelson was brought back to full physical functioning and emotional balance by a postmastectomy program that has been operating here since 1976.

Sponsored by the National Council of Jewish Women and the Young Women's Christian Association of Hackensack, the Bergen County Postmastectomy Program is operating out of the Jewish Center here. Most of the staff are volunteers, and professional therapists also donate their services.

This project, which is free, has been so successful that programs modeled on it have sprung up in three other counties in the state. The Young Women's Christian Association has gone nationwide with 245 postmastectomy programs called Encore, which include exercises, swimming and discussion.

Here, a postmastectomy group usually is made up of 15 women who work out with a physical therapist in the pool and gymnasium. A psychologist offers group therapy once a week. Each series lasts eight weeks.

"That's enough," said Shirley Hart, the co-founder of the group, who had a double mastectomy. "We do want to discourage dependency, and we have found that eight sessions are adequate time to recover physically." After six months, there is a reunion so that the program and the participants' progress can be evaluated.

During one of the reunions, Ruth Cowan, a physical therapist, was helping some women in the Jewish Center pool. She was gently stretching once-immobile arms up and backward and rotating others in the water, murmuring encouragement.

"Take a look," she told one newcomer. "This is where you're going to be. Are you doing your exercises every day? Look, I don't blame you for trying to protect yourself."

All of the other members of the group had regained their arm action.

"After I had my mastectomy, I couldn't close the car door," Mrs. Nelson said. "I couldn't reach glasses on the shelves or hang the wash."

When participants arrive at the Jewish Center, "they undress with other women who have had the same trauma," Mrs. Hart said. "They are curious how the others look, and their physical shame starts to pass away. They see that it is not so horrible, that they aren't freaks."

Some of these in the reunion group were bitter about their surgeons' after-surgery instructions, calling them "haphazard" and "not done properly."

Cowan said that most doctors' staff members "don't have the knowledge of body mechanics" that will bring the patient back to full movement.

At first, some doctors in the area opposed the postmastectomy program, but seeing the results, most now support it.

The emotional damage following a mastectomy also needs to be addressed.

The most intense feeling brought to the therapy discussions is the fear of death.

"It's still a killer, still extremely frightening," Dr. Mildred Swinson, a psychologist who steers the therapy group, said. "In addition, mothers with daughters are worried about them, because, according to the American Cancer Society, the risk is two to three times as great that daughters of women who have had breast cancer will also develop breast cancer.

"The mother feels guilty," Dr. Swinson said. " 'Will I pass it on to her?' she asks. The daughter tends to blame the mother. This can produce terrible strains."

Another problem, Dr Swinson said, was "the tremendous rage against doctors."

"They had to blame someone for this destruction," she said, adding, "I think the media have done a great job in informing the public that a mastectomy is believing for now at least, that to be surgical procedure."

[From the Richmond Times-Dispatch, Thursday, Mar 24, 1983]

Cancer Patient's Spouse Also Needs Support, Researcher Says

(By Beverly Orndorff)

San Diego.—Learning to live with cancer is difficult, but learning to live with someone else's cancer may be more difficult.

That, at least, is suggested by an ongoing study at New York's Memorial Sloan-Kettering Cancer Center that indicates that cancer may be harder on the patient's spouse than on the patient during the early phase of the illness.

"Who supports the supportgiver?" asked Marilyn T. Oberst, director of nursing research at Sloan-Kettering, in a talk at an American Cancer Society seminar.

The answer may well be, in many cases, "No one," Ms. Oberst said.

And while there has been research on the effects of cancer in its final phases on the patient's family, there is practically none on the early phases, she said.

In her study of newly diagnosed cancer patients and their spouses, Ms. Oberst is finding that the spouses show high anxiety levels and generally don't cope as well as the patients after the patients come home from the hospital.

The patients in the study have cancers of the bowel and genitourinary system. Patients and spouses are interviewed before discharge from the hospital, then 10, 30 and 60 days later.

Tests for anxiety levels and coping ability are given. In general, the patients' anxiety levels are highest, and their coping scores are lowest within the first 10 days after leaving the hospital, according to Ms. Oberst's study.

For the spouses, coping effectiveness begins declining after the first 10 days and continues for at least the next two months. Ms. Oberst said interviews will be made at three- and six-months intervals.

"As the patients improve, the spouses begin to report their own feelings of increasing fatigue and become progressively less able to handle problems of everyday living," she said.

The spouses felt that they lacked support from all sources, Ms. Oberst said.

"NOBODY UNDERSTANDS"

"They said again and again in many different ways, 'Nobody understands what I'm going through. He's feeling better and I keep feeling worse. Everyone pats him on the back and says how well he's managing, no one asks about me.'"

The study suggests, Ms. Oberst said, that "We need to do better in preparing patients for discharge. . . . And we need to talk a lot more with the spouses."

In another report yesterday, a New York University biochemist suggested that food seeds, such as rice, corn, chickpeas and beans, may contain a substance that protects against cancer.

The substance, said Dr. Walter Troll, is called protease inhibitor, and it essentially decreases the amount of protein available for digestion in our bodies.

WORLDWIDE STUDIES

Studies of various populations around the world show varying incidences of cancer, suggesting that dietary factors may be involved, Dr. Troll said.

Countries that have high protein diets—that is, countries where meat consumption is high—have relatively high incidences of breast, colon and prostatic cancers, Dr. Troll said. Thus, substances that reduce protein digestion may confer some protection against those types of cancer.

According to Dr. Troll, all seeds—including canned beans and corn—have high levels of protease inhibitors. He cautioned, however, that his studies are still in an early stage, and he noted the complexity involved in studying nutrition and cancer.

"The question of which factors in nutrition are mot decisive in the Western diet that contribute to the high occurrence of cancer has not been settled," he said.

[From the Richmond Times-Dispatch, Sunday, Jan 24, 1982]

PSYCHOLOGICAL IMPACT OF CANCER USUALLY SEVERE

(BY DR. W. GIFFORD-JONES)

How do most people react when the doctor tells them they've got cancer? This year, 900,000 North Americans will receive this diagnosis. Families and friends should be aware of the various ways patients respond to this shocking news.

Hearing a physician say, "We've found a malignancy," poses a unique and special threat. Usually a predictable series of disorganized thoughts flies through the mind. How will family and friends react? Will we be treated differently and possibly isolated? Will there be loss of esteem? Will it affect our body image, sex lives and lifestyle? Will we die? And how soon?

How one responds to cancer depends partly on which organ is involved. The Memorial Hospital for Cancer and Allied Diseases studied this problem. Dr. Arthur M. Sutherland reports in the Cancer Journal for Clinicians that colostomy patients often fear the disapproval of society, as they once worried about criticism from a toilet-training mother.

For example, one patient was described by her family as a "crazy-clean housekeeper." She developed cancer of the rectum and reluctantly agreed to surgery. But

when the operation required a colostomy she became depressed and contemplated suicide. She believed she was unacceptable to friends and eventually isolated herself. To her, life became worthless.

Predicting how a patient will react is an uncertain task. Many of us would be hard-pressed to know what goes on in the mind of a best friend under normal circumstances. It's therefore difficult for surgeons to forecast how people will compensate for the loss of heart, leg or bowel function. There's a wide range of possibilities.

The initial response is often a refusal to accept the diagnosis. Fear of cancer is so intense that it must be removed from consciousness. The patient rationalizes that the doctor is wrong. Conversely, the threat to existence may be so overwhelming that some patients want to rush headlong into surgery. Others find a dozen illogical reasons to postpone an operation. They ask, "Why mutilate my body if I'm going to die in a few months anyway?"

Patients may fall into one of several pitfalls after surgery. One man was convinced the cancer of the prostate gland he had developed was a form of punishment. During his life he had enjoyed several extra-marital affairs. Now he felt he was reaping the reward of immoral behavior.

The Memorial Hospital study cites another problem. Hypochondriacs, those who fear disease, usually approach surgery expecting the worst to happen. Post-operatively, many believe that irreparable damage has been done. They are convinced that removal of any part of their body decreases vital energy, thus rendering them more susceptible to the recurrence of malignancy. As a result, they rigidly restrict all activity.

This restriction is considered by them to be a lifesaving scheme. It is a pattern that is difficult for physicians to break. As one patient remarked, "I treat my body like an old car. I expect it to break down any minute."

Some hypochondriacs develop paranoid reactions. They're convinced the surgeon made an error, or that the operation was more extensive than it needed to be. Such thoughts can lend descent into depression, and on rare occasions suicide.

Obsessive-compulsive reactions are usually seen in patients who have rectal surgery resulting in colostomy. All patients who undergo colostomy develop this to some degree. But those who were compulsive about body habits prior to surgery have experience exaggerated reactions. One man was compelled to spend hours every day irrigating the colostomy. He needed to be sure it was clean before seeing friends.

Families should realize that some cancer patients are very demanding. They often complain of minor symptoms and aggravations. This is an attempt to distract themselves from the anxiety of cancer and possible death.

It's been said that "fear is the greatest of all inventors of minor post-operative complication may be perceived by the patient as a recurrence of malignancy. A few words of explanation by doctors and nurses can prevent hours or days of anguish. Similarly, experienced enterostomal therapists could now ease the apprehension of colostomy. But most of all, helpful and supportive families or friends can help the patient make a gradual adjustment to the diagnosis of cancer.

[From the Richmond Times-Dispatch, Sunday, Apr. 29, 1984]

Terminally Ill Patient: Multifaceted Problem

(By Beverly Orndorff)

It is an issue that has come out of the medical closet. It is a matter that physicians are talking about openly, in regular medical school conferences and in journals.

The issue is, what is the physician to do for the hopelessly ill patient? Until recent times, there was little that physicians could do other than let nature take its course. Now, medicines and machines can significantly retard the dying process, and physicians, whose training instills in them a reflexive inclination to preserve life, are realizing there are times when such measures ought to be withheld.

One reflection of the open discussion of such issues is a recent report in the New England Journal of Medicine, prepared by 10 experienced physicians from around the nation, including Dr. Edward W. Hook, chairman of the University of Virginia Medical School's department of medicine. The report was based on a two-day meeting of the 10 physicians in Boston last fall that was convened by the Society for the Right to Die.

Dr Daniel D. Federman, professor of medicine at Harvard Medical School and past president of the American College of Physicians, was chairman of the meeting, which was called to develop guidelines for physicians in dealing with terminally ill patients.

Two precepts were the center of the discussions, according to the physicians' report. One is that the patient has a paramount role in making decisions about his or her treatment. The other is that aggressive treatment of a hopelessly ill patient only prolongs a difficult and uncorfortable dying process.

Ideally, the physicians said that decisions about medical treatment should be made by the patient. But there can be a variety of circumstances that cloud a patient's judgment, including drugs, pain, and the disease itself. In such cases, the report indicated, "the physician must rely increasingly on the presumed or prestated wishes of the patient." A previously written statement by the patient, expressing his or her wishes about treatment in the terminal stages of an illness, would be helpful, according to the physicians.

Such expressions are recognized in 15 states and the District of Columbia (Virginia is one of those states, the report stated). If there are no such written expressions, the physicians continued, the physician must determine from family members and friends the "attitudes and wishes the patient would have expressed had competence been maintained."

Another confusing factor can be the uncertainty of diagnosis, that the patient indeed does have the illness that the physician believes he or she has, and the uncertainty of the patient's prognosis. If the physician is not an expert in the patient's illness, he or she should consult with those who are, the report suggested. If there is disagreement about the diagnosis or prognosis, life-sustaining measures should be maintained until the issue is resolved.

"The rare report of a patient with a similar condition who survived is not an overriding reason to continue aggresive treatment," said the physicians' report. "Such negligible statistical possibilities do not outweigh the reasonable expectations of outcome that will guide treatment decisions."

The report strongly urged physicians to discuss the diagnosis of life-threatening illnesses with their patients. "Although some physicians and families avoid frank discussions with patients, in our view, practically all patients, even disturbed ones, are better off knowning the truth. A decision not to tell the patient the truth because of fear of his or her emotional or psychological inability to handle such information is rarely if ever justified . . . The anxiety of dealing with the unknown can be far more upsetting than the grief of dealing with a known, albeit tragic, truth," said the report.

It also stressed that the physician must help the patient understand and deal with the news of a poor prognosis, through reassurance that the patient will not be abandoned and that there are supportive measures that can be taken. The physician also must be prepared, the report stated, to share his or her personal opinions about what the patient should do. "Patients often ask a trusted physician, 'What would you do?' A direct answer is in order," the 10 physicians agreed.

They offered recommendations for specific types of cases. The generally alert patient who is dying of, say cancer, ought to be agressively treated to relieve pain and suffering. The level of care should reflect an understanding between physician and patient, with occasional reassessment, according to the physician's report. In many instances, the patient or his or her family may not wish to receive emergency resuscitation; the prime desire is for comfort.

For patients in a definitely established, persistent vegetative state, the physicians suggested that it is morally justifiable to withhold antibiotics and artificial feeding and hydration measures, as well as other forms of life-sustaining treatment, thus allowing the patient to die.

"This obviously requires careful efforts to obtain knowledge of the patient's prior wishes and the understanding and agreement of the family," said the physicians' report.

One thing is clear from the New England Journal report. The matter of what to do in the face of terminal illness is more than a physicians' issue.

It is one that each of us should face squarely because, as the 10 physicians repeatedly emphasized, it is our desires as patients, if and when we have a terminal illness, that are the ultimate guidelines that physicians seek.

APPENDIX 2.

[Submitted for the record by Dr Charles Hubray]

ANTIESTROGEN-CYTOTOXIC CHEMOTHERAPY AND BACILLUS CALMETTE-GUERIN VACCINATION IN STAGE II BREAST CANCER

72-MONTH FOLLOW-UP

C.A. Hubay, M.D.[a], N.H. Gordon, Ph.D.[a], J.P. Crowe, M.D.[a], S.P. Guyton, M.D.[a], O.H. Pearson, M.D.[b], J.S. Marshall, M.D.[b], E.G. Mansour, M.D.[c], R.E. Hermann, M.D.[d], J.C. Jones, M.D.[e], W.J. Flynn, M.D.[f], C. Eckert, M.D.[g], R.W. Sponzo, M.D.[h], W.L. McGuire, M.D.[i], D. Evans, M.D.[j], and 24 Participating Investigators

Department of Surgery[a], Department of Medicine[b], Case Western Reserve University School of Medicine and University Hospitals; Cleveland Metropolitan General Hospital[c], Cleveland Clinic Foundation[d], St. Luke's Hospital[e], Cleveland, Ohio; Youngstown Hospital Association[f], Youngstown, Ohio, Albany Medical College[g], Albany, New York; Albany Regional Cancer Center[h], Albany, New York; University of Texas Health Science Center[i], San Antonio, Texas, and Akron General Medical Center[j], Akron, Ohio.

Supported by NIH Contract CB-23922 (Formerly CA-43990) (CAH) and NIH Grant CA30295 (WLM)

Address for reprints: C.A. Hubay, M.D., Department of Surgery, 2074 Abington Road, Cleveland, Ohio 44106.

ABSTRACT

A prospective randomized clinical trial of adjuvant treatment of 312 stage II breast cancer patients utilizing chemotherapy, anti-estrogen therapy, and immunotherapy is reported at 72 months follow-up. Stratification of patients was based on nodal involvement and estrogen receptor assay of the primary tumors. Findings at 72 months indicate that antiestrogen therapy (Tamoxifen*) added to CMF chemotherapy resulted in significant delayed recurrence in ER+ postmenopausal patients, ER+ patients with 4 or more positive nodes, and ER+ patients with tumors greater than 3 cm. in diameter. The addition of nonspecific immunotherapy with BCG had no effect on disease-free survival. Estrogen receptor and progesterone receptor measurements in primary breast cancer provide valuable prognostic information on subsequent recurrence and overall survival and should be documented in future clinical trials.

*Nolvadex

ANTIESTROGEN-CYTOXIC CHEMOTHERAPY AND BACILLUS CALMETTE-GUERIN VACCINATION IN STAGE II BREAST CANCER

72-MONTH FOLLOW-UP

For the past eight years we have been conducting a prospective randomized clinical trial of the adjuvant treatment of 312 surgically treated stage II breast cancer patients. Chemotherapy (CMF) antiestrogen therapy (Tamoxifen)*, and Bacillus Calmette-Guerin (BCG) immunotherapy were utilized in the trial, which was the first study in which patient stratification was based on the presence or absence of estrogen receptors in the primary tumor.

These studies conceived in the early 1970's began in 1974. It was postulated that breast cancer cells beyond the confines of the operative site might be successfully eradicated at a time when the total tumor burden was low. Adjuvant therapy thus might prove to be beneficial in decreasing recurrence and increasing patients' survival. This report is a summary of results in stage II breast cancer patients entered into this multi-institutional clinical trial following its inception.

The details of the various treatments under this protocol have been published, along with results after 48 months and 60 months follow-up (28-31,53). The early results can be summarized as follows: (1) Women whose breast cancers contained low or undetectable (< 3 fm/mg cytosol protein) estrogen receptors (ER-) recurred more rapidly, regardless of the treatments used, than those patients whose tumors did contain estrogen receptors, (ER+) (≥ 3 fm/mg cytosol protein).

*Nolvadex®

(2) In comparing the three adjuvant regimens used in the study, none appeared to offer any advantage for the ER- group.
(3) Women whose breast cancer contained estrogen receptors (ER+) had a prolongation of disease-free interval when their treatment included the antiestrogen, Tamoxifen.
(4) Overall survival was significantly longer in ER+ patients when compared with ER- patients. Since there were no untreated controls, the study left unanswered the question of whether or not the chemotherapeutic regimen employed was of any advantage. We now report follow-up data on recurrence and mortality up to 72 months.

Materials and Methods

Patient selection, stratification and randomization, treatment regimen, methods of follow-up and statistical evaluations previously reported in detail will be briefly reviewed. The study group consisted of 318* women undergoing radical or modified radical mastectomy for primary stage II breast cancer. Estrogen receptor assays were performed on the primary tumor in all patients, mainly by one laboratory (Wm. McGuire's). Only those patients found to have one or more axillary lymph nodes involved with tumor were considered eligible for inclusion. Informed written consent was obtained from eligible subjects prior to randomization.

The patients were stratified both by ER category (positive or negative) and by the number of axillary nodes found to contain tumor by pathologic staging (1-3 or $\geq$ 4 positive nodes). Within each

*Of the original 318 patients, six were initial protocol infringements, thus, 312 patients have been followed since inception of the study.

stratum patients were then randomly assigned to one of three treatment modalities: 1) cytoxan, methotrexate and 5-fluorouracil (CMF), 2) CMF plus Tamoxifen (CMFT) ; and 3) CMFT plus Bacillus Calmette-Guerin vaccination (CTB).

In 1974 when the study was initiated, an untreated control group was included. In 1976, however, after Bonadonna's promising report (4), the control group was changed to CMF therapy. Our CMF treatment was similar to that reported by Bonadonna, except for a somewhat smaller initial dosage of drugs. Cytoxan* (60 mg/M^2) was given orally during days 1 through 14, for each of 12 monthly cycles. Methotrexate† (25 mg/M^2) and 5-fluorouracil‡ (400 mg/M^2) were given intravenously on days 1 and 8 for 12 monthly cycles. The doses of the chemotherapeutic agents were escalated until myelosuppression became evident. Tamoxifen (Nolvadex)§ was administered orally (20 mg) twice daily for one year (40 mg/day). In the group receiving immunotherapy, vaccinatons with BCG|| were carried out in the second year as follows: weekly the first month and then monthly the following eleven months.

Physical examinations and blood chemistries were performed at three-month intervals. Routine chest x-rays were taken at six-month intervals, and bone scans and mammograms at yearly intervals. The end-point for a study patient was the first documented recurrence or second primary. Therapy after recurrence was left to

*Mead Johnson, Evansville, Indiana
† Lederly Parenterals, Inc., Caroline, Puerto Rico
‡ Hoffman-LaRoche, Nutley, N.J.
§ Nolvadex was donated by ICI Americas, Inc.
|| Tice (University of Illinois): 5 + 3 x 10^8 C.F. (colony forming units)/ Institutes of Health, Bethesda, Md.

the discretion of the physician in charge of the patient. Patient accession was terminated in June, 1979.

All basic information, including the clinical characteristics of the patient and her tumor has been entered into a computer for retrieval, follow-up and analysis. The statistical methods (8,21,67) for evaluation of results have been previously reported and consisted of life table analysis (22) using product-limit estimates and pair-wise comparisons made with the generalized Wilcoxon test. For assessment of delay in recurrence, the percentile ranks were obtained and compared. Delay was defined as the difference of the percentile ranks of the given two groups which were being compared. Approximate p values were obtained for this comparison (25). This delay was obtained at the first quartile (the 25th percentile rank) and whenever possible at the second quartile (median).

Between September, 1974 and June, 1979, 318 patients with stage II breast cancers were entered into this multi-institutional adjuvant clinical trial. Seventy-four percent had ER levels ≥ 3 femtomoles/mg cytosol protein. Of the original 318 patients, six were protocol infringements and thus 312 patients have been evaluated since the inception of the study. One hundred one were randomized to CMF therapy, 110 CMFT and 101 patients CMFT followed by BCG vaccinations during the second year (CMFT-BCG).

Prognostic variables, including age, number of axillary nodes involved by tumor, size of tumor, ER values, menopausal status and dosage of chemotherapy were documented for all treatment groups. None of these were strikingly different among the three groups.

All patients completed their primary therapy by June, 1979. Four patients receiving BCG immunization during 1979-80 are now 24 months post treatment and are included in this report. Patient compliance with protocol requirements has been unusually good. To date, five patients have been lost to follow-up. Four of these patients completed therapy, but cannot be traced 14 months to 48 months postmastectomy. One patient was randomized, then refused treatment. In 1981 she was alive four and one-half years postmastectomy, but is now listed as lost.

Nineteen patients withdrew from the study for personal reasons, most of whom received chemo-endocrine therapy for 12 months and then elected to stop additional therapy. Twenty-three patients are classified as protocol infringements of major or minor nature, or intolerance to drugs. For statistical purposes, these patients are evaluated to the date of withdrawal only. All are followed for survival whenever possible.

Results

As previously noted, early in the study, five patients (controls) were randomized to no adjuvant therapy following surgery. All are dead except one patient who recurred at 13 months and was placed on Tamoxifen with response. She is alive eight and one-half years postoperatively on Tamoxifen maintenance.

Chemotherapy, in general, was well tolerated, but the dose levels of the drugs had to be altered transiently in some patients, owing to myelosuppression. In no instance was leukopenia severe and intercurrent infections resolved without sequelae. Alopecia was mild, rarely requiring the use of wigs. The most common

complaints following intravenous therapy were nausea, fatigue and malaise for one or two days. No serious metabolic derangements occurred, with most patients gaining weight at an average of ten pounds while on chemotherapy. Tamoxifen, the antiestrogen agent used, was surprisingly well tolerated, with most patients experiencing hot flashes. Some patients noted vaginal dryness, which was easily controlled by creams. Immunization with BCG resulted in local symptoms at the site of injection and some patients experienced delayed generalized arthralgias easily controlled by non-narcotic analgesics.

As of September 1, 1982 there had been 119 recurrences among the patients remaining in the study, 44 in the CMF group, 42 in the CMFT, and 33 in the CMFT-BCG groups.

In those patients completing therapy there have been 73 deaths to date: 24, 31, and 18 respectively in the CMF, CMFT, and CMFT-BCG groups. X^2 analysis shows no statistical difference among the three treatments. All patients died of metastatic breast cancer.

Five additional patients died of nonmetastatic disease: 2 of myocardial problems, 32 and 29 months postoperatively; 2 died of cerebral vascular accidents, 61 and 64 months postoperatively; one died of supposed aplastic anemia 35 months postoperatively.

There have been 19 deaths in patients withdrawing from study: 11 were patients treated with CMF, 5 with CMFT, and 3 in the CMFT-BCG group. There is no significant difference (X^2 test) between the number of deaths in the three treatment groups.

Figure 1 depicts the cumulative rate of recurrence of all ER+ and ER- patients. Recurrence continues to be more frequent for the ER- patients than for ER+ patients (p=.0003). It should

be noted that the rate of recurrence in the ER- patients was rapid for the first 24 months (41.8%) and then diminished to a more constant rate.

In contrast, the ER+ patients fared better during the first 24 months of study, and only after 12 months when treatment was stopped was recurrence noted. Whether this reflects the effect of therapy or an inherently better prognosis in this group is speculative since so few control patients were studied. The recurrence curves followed for 72 months continue to show lower recurrence for ER+ patients.

Figure 2 compares cumulative recurrence of all patients (estrogen receptor status not considered). Since statistical evaluation of the CT and CTB groups showed identical recurrence rates, the two groups have been combined for comparison with the chemotherapy alone group in Fig. 2. At 72 months, the group treated with CMF alone exhibited the highest recurrence. Those treated with Tamoxifen (CT) or Tamoxifen and BCG (CTB) show an initial delay in recurrence, followed by a more constant rate of recurrence to 72 months. At the 33, 45, and 48-months follow-up reports, the latter two groups had a significant delay in recurrence when compared with the CMF treated group.

The combined curves continue to show an advantage for Tamoxifen therapy in delaying recurrence. The September, 1981 analysis of the data (31) showed a difference ($p=.02$) between the curves. September, 1982 data analysis continues to show an advantage for the Tamoxifen treated patients, however, the p value is now $p=.11$.

When the recurrence rates in each of the treatment categories of ER+ patients are compared by life table analysis (Fig. 3), there remains an advantage for the antiestrogen treated groups in recurrence delay, but of borderline significance (p=.08) when compared with September, 1981 findings (p=.048). Quartile analysis of delay of recurrence is 10.3 months at the first quartile (p=.024) and is greater than 6.8 months at the second quartile (Table I). In contrast, the ER- patients (Fig. 4) appear to receive no benefit from antiestrogen therapy.

The relationship of recurrence to menopausal status has been documented for the entire group. There are no differences in recurrence at this stage of follow-up. Stratification by estrogen receptor status, however, reveals differences in recurrence at 72 months: premenopausal ER+ 40.2% vs. ER- 48% (p=.09, Fig. 5); postmenopausal ER+ 59.5% vs. ER- 70.4% (p=.001, Fig. 6), showing more rapid recurrence for ER- patients in both groups.

Using life table analysis, there appears to be no difference among treatment regimens in the ER+ premenopausal patients (p=.41). It should be noted, however, that when Tamoxifen is added to CMF treatment, there is a 8.6 month delay in recurrence at the first quartile (p=.0095) (Table 1). This delay in recurrence, early in their follow-up, may be a reflection of small sample sizes rather than a true difference among the regimens and final analysis awaits prolonged follow-up.

Figure 7 shows the treatment comparison of cumulative recurrence for ER+ postmenopausal patients. Both Fig. 7 and Table I document a significant delay of 11 months in recurrence (p=.008) for the first quartile, when Tamoxifen is added to the

treatment regimen, and greater than 20 months for the second quartile, both highly significant.

The overall recurrence between patients with 1-3 positive nodes and patients with ≥ 4 positive nodes is shown in Fig. 8. The lower rate of recurrence in patients with 1-3 positive nodes is consistant with previous observations on such patients (22).

When treatments of ER+ patients with 1-3 positive nodes are compared, there is no advantage of any regimen (Fig. 9, Table I). In ER+ patients with ≥ 4 positive nodes (Fig. 10), an unexpected finding was the lower recurrence rate in the Tamoxifen treated patients ($p=.05$). Quartile analysis (Table I) shows a significant delay of nine months in these patients. No similar benefit was noted for the ER- patients with ≥ 4 positive nodes.

Figure 11 compares treatments in ER+ patients whose primary tumors were greater than 3 cm. in diameter. There is a significant delayed recurrence advantage for the regimens containing Tamoxifen ($p=.00023$), Table I. No such advantage was noted for ER+ tumors less than 3 cm. or for ER- patients. The reasons for these findings remain obscure, but may result from the "Compertzian" affect as pointed out by Fisher (17).

Figure 12 depicts the cumulative survival between ER+ vs. ER- patients ($p=.0001$). The longevity advantage continues with the ER+ patients whose survival is 67% compared with 44% for the ER- patients at 72 months.

Comparison of data of all ER+ patients treated with or without Tamoxifen does not show a difference in overall survival at this stage of follow-up. Comparison of survival for ER+ patients with

1-3 or ≥ 4 positive nodes, with or without Tamoxifen, are not statistically different. Continued follow-up should answer survival effects of the antiestrogen therapy, as total deaths to date are small in number.

Discussion

The surgical "cure" rate continues to be consistently high for stage I breast cancer patients (negative axillary nodes). Crowe (14) has pointed out, however, that menopausal status and estrogen receptors offer additional prognostic factors for this group as well. In an effort to reduce or delay recurrence in stage II breast cancer, known to be considerable, combination chemotherapy, antiestrogen therapy and nonspecific immunotherapy with BCG was studied in similar patients. At the outset of this trial (1974), we had hoped to compare women treated with adjuvant chemo-antiestrogen therapy with women treated by surgery alone. A correlative objective was to document what effect, if any, antiestrogen therapy could have on recurrence and survival. In 1976, however, Bonadonna's (4) promising initial report with CMF adjuvant therapy led us to change our planned therapy and treat all patients with CMF, i.e., no control group. It was early in the study, however, and few such patients were affected.

Over the last two decades, cytotoxic chemotherapy has been shown to effectively palliate disseminated breast cancer in a high percentage of afflicted women. For more regional disease, Cooper (13), Fisher (17,18), Bonadonna (5,6,7) and many others have added valuable knowledge to breast cancer treatment. The value of

adjuvant therapy, however, has been on less firm ground and may reflect our clinical inability to determine systemic spread at the time of initial surgical decision making.

In all long term studies of patients receiving chemotherapy, there is concern of development of secondary malignancies owing to immunosuppression or chemical induction. Twelve of 312 stage II breast cancer patients treated as previously outlined have developed second malignancies 13-80 months postmastectomy. Three were myeloproliferative disorders arising 48, 72, and 80 months postoperatively. Four were new carcinomas of the contralateral breast, two were colon cancers, and one each of the endometrium, cervix and lung. Table II summarizes tumor types, original estrogen receptor status and protocol therapy. The spectrum of malignancies observed, however, seems unrelated to therapies and bears no relationship to receptor status. We continue to follow living patients and will monitor all developing medical problems.

The first established usefulness of alteration of human sex-steroid hormones in breast cancer was made by Beatson (2). His therapeutic oophorectomy for disseminated breast cancer on June 15, 1895 (published in Lancet, 1896) seemed a medical triumph. In one patient he reported "all vestige of the previous cancerous disease had disappeared" postoperatively at eight months. Thus, by scientific observations of cattle castrated to prolong milk production by farmers in his area, and to some extent by serindipity, Beatson laid the cornerstone for hormone manipulations of human cancers. It is indeed fortunate that his first patient responded so dramatically, as we know today that in only 40%

of premenopausal women with advanced breast cancer will castration be of value. This response rate can be improved to near 60% if estrogen receptor positive stage IV breast cancer patients are treated by hormones, oophorectomy, hypophysectomy, or adrenalectomy (9,34,35,42,54,62).

Recently, potent nonsteroidal antiestrogen compounds have been developed which appear to be clinically effective by competitive binding to cytosol estrogen receptors in breast cancer cells. These compounds appear to inhibit entry of estrogens into target sites rather than by suppressing secretions.

Numerous investigators (3,10,15,16,19,23,24,26,32,33,36,37,38,40,45-52,55-61,63,65,68-71) have documented trials with antiestrogens such as Tamoxifen and Nafoxidine and most report remissions and delay in recurrence. Recently, Hayward (27) and Stoll (66) have summarized developments in the endocrine treatment of cancer and there appears to be little doubt that estrogens are predominent in stimulating the growth of certain human breast cancers.

The findings of this prospective randomized trial of adjuvant therapy in stage II breast cancer patients continue to show that the antiestrogen drug Tamoxifen, along with CMF chemotherapy, significantly delays recurrence in postmenopausal women with ER+ breast cancers and ER+ patients with 4 or more positive nodes and tumors > 3 cm. In a recent preliminary report, Fisher (19) has confirmed that Tamoxifen given with 2-drug chemotherapy is more effective than 2-drug chemotherapy alone in delaying recurrence in postmenopausal women with stage II ER+ breast cancer after two years of follow-up.

Although the correlation of estrogen receptors and the response rate to cytotoxic chemotherapy in metastatic breast cancer is as

yet somewhat conflicting (1,12,35,39,41) more recent data suggest that at least in ER+ stage IV breast cancer patients, an initial trial of hormone therapy appears to be justified without compromise for subsequent chemotherapy.

It was noted early in this study that recurrence be[redacted] manifest in ER+ patients after therapy with Tamoxifen [redacted] 12 months, leading us to postulate that more prolonged therapy might have been of further benefit. This is being evaluated in our present clinical trial.

Progesterone receptors (PgR) in 189 of our study patients were recently reported by Clark (11). It was noted that PgR levels yielded significant prognostic information in this group of patients, independent of the therapies utilized. Multivariate regression analysis of this data revealed that PgR and the number of positive nodes remained significant in predicting disease-free survival, whereas ER was no longer significant when PgR was in the model. However, PgR and ER levels are highly correlated. We urge that ER and PgR levels be measured in all future clinical trials.

The investigators will be forever grateful to the brave women volunteering for this study. Most of them became boosters of the program and were helpful in allaying the fears and anxieties of women hesitant to accept randomized therapy. Their courage and confidence was inspiring to all and has helped the investigators immeasurably.

SUMMARY

A prospective randomized clinical trial of adjuvant treatment of 312 stage II breast cancer patients using chemotherapy, antiestrogen therapy and immunotherapy is reported to 72 months. Median follow-up is 41.3 months. The following conclusions seem warranted:

1. Estrogen receptor positive (ER+) stage II postmenopausal patients had delayed recurrence when Tamoxifen was added to CMF adjuvant therapy.
2. The addition of Tamoxifen to adjuvant chemotherapy (CMF) significantly delayed recurrence at six years in stage II ER+ patients with 4 or more positive axillary lymph nodes.
3. The addition of Tamoxifen to CMF therapy significantly delayed recurrence at six years in stage II ER+ patients with tumors greater than 3 cm. in diameter.
4. ER+ stage II patients with 1-3 positive axillary nodes and estrogen receptor negative (ER-) patients showed no benefit at six years from addition of Tamoxifen to CMF therapy.
5. The addition of nonspecific immunotherapy with BCG, had no discernable effect on disease-free survival.
6. Estrogen receptor and progesterone receptor measurement of the primary tumor provides prognostic information on recurrence and survival and are important parameters to be documented in all future adjuvant trials.

Legends

Fig. 1 Cumulative recurrence of 312 stage II breast cancer patients stratified by estrogen receptor assay. Estrogen receptor positive (ER+), n=234; estrogen receptor negative (ER-), n=78.

Fig. 2 Cumulative recurrence of 312 stage II breast cancer patients by treatment. Here all tamoxifen treated patients are combined and compared with chemotherapy only group (see text). C, n=101, CT and CTB, n=211.

Fig. 3 Cumulative recurrence of ER+ patients with and without Tamoxifen added to therapy. C, n=76; CT and CTB, n=158.

Fig. 4 Cumulative recurrence of ER- patients. CT and CTB groups with antiestrogen therapy. C, n=25; CT and CTB, n=53.

Fig. 5 Cumulative recurrence of premenopausal patients stratified by estrogen receptor assay. ER+, n=64; ER-, n=30.

Fig. 6 Cumulative recurrence of postmenopausal patients stratified by estrogen receptor assay. ER+, n=170; ER-, n=48.

Fig. 7 Cumulative recurrence of ER+ postmenopausal patients with and without added Tamoxifen. Quartile analysis shows significant delay in recurrence with antiestrogen therapy (Table I) C, n=49; CT and CTB, n=121.

Legends, continued

Fig. 8 Cumulative recurrence of 312 breast cancer patients stratified by nodal involvement following pathologic staging. 1-3 nodes, n=146; 4 or more nodes, n=166.

Fig. 9 Cumulative recurrence of ER+ patients with 1-3 positive axillary lymph nodes by treatment regimens. C, n=36; CT, n=40; CTB, n=37.

Fig.10 Cumulative recurrence of ER+ patients with 4 or more positive axillary lymph nodes by treatment regimens. CT and CTB combined Tamoxifen groups. C, n=40; CT and CTB, n=81.

Fig.11 Cumulative recurrence of ER+ patients with tumors greater than 3 cm. in diameter treated with CMF or added Tamoxifen (CT and CTB), C, n=34; CT and CTB, n=66.

Fig.12 Overall life table analysis of deaths stratified by ER assay. Note worse prognosis for the ER negative patients (p=.0001). Both groups similarly treated (see text) ER+, n=234; ER-, n=78.

RECURRENCES - SEPTEMBER, 1982

GROUP	QUARTILE	CMF (mos)	CMF TAMOXIFEN (mos)	DELAY (mos)	P* VALUE
ER+	1	25.2	35.3	10.2	.024
	2	65.2	>72	>6.8	---
ER+; 1-3 positive nodes	1	70.0	66.2	-3.8	.99
ER+: 4+ positive nodes	1	21.2	30.3	9.1	.0034
	2	40.1	49.6	9.4	.023
ER+: tumor diameter >3 cm.	1	21.1	30.8	9.7	.00023
	2	40.8	>72	>31.2	---
ER+: premenopausal	1	30.5	39.1	8.6	.0095
ER+: postmenopausal	1	24.2	35.3	11.1	.0086
	2	50.7	71.4	20.7	<.000001

*Computed for a one tail test

TABLE I. First and second quartile (in months) of the recurrence cumulative distribution function of the CMF and CMF + Tamoxifen treatment regimens. Delay is defined as the difference between the quartiles of these two regimens.

SECOND PRIMARY TUMORS

PATIENT	TUMOR TYPE	DIAGNOSIS (MONTHS POSTMASTECTOMY)	ORIGINAL PROTOCOL THERAPY	ORIGINAL ER STATUS
I.C.	Lymphocytic lymphoma	80 months	CMF	Positive
A.C.	Chronic Leukemia	72 months	CMFT + BCG	Negative
G.L.	Rectal Carcinoma	21 months	CMFT	Positive
S.K.	Contralateral Breast	51 months	CMFT	Negative
A.L.	Endometrial Carcinoma	60 months	CMFT	Negative
J.J.	Lymphoma	48 months	CMF	Negative
M.M.	Lung Carcinoma	18 months	CMFT	Positive
E.P.	Contralateral Breast	13 months	CMF	Positive
M.R.	Contralateral Breast	24 months	CMFT + BCG	Positive
S.S.	Contralateral Breast	54 months	CMFT	Positive
E.V.	Colon Carcinoma	14 months	CMF	Positive
C.C.	Cervix Carcinoma	77 months	CMFT + BCG	Positive

TABLE II. Occurrence of second primary tumors in 312 patients receiving adjuvant therapy following surgery for stage II breast cancer.

ACKNOWLEDGEMENTS

The authors thank all other surgeons whose patients were entered into this collaborative study. We also thank the following nurse clinicians: Rody Brodhead, Catherine Damm, Lib Fisher, Robin France, Ginny Gibbons, Ethel Gray, Ina Hardesty, Belva Hardin, Norma Jarmusch, Marge Norder, Angela Sheehan, Michele Trombly, Nancy Urbancic, and Roxia Wolfe. We thank Jane Brumberg, the Administrative Coordinator; Bertha J. Adams and Theresa Courtland for secretarial assistance. Our thanks to the following data managers: Linda Bonaquisti, Barbara Domyan, and Noreen Radlowac. Also Ann Merrell, Thomas George, Joan Holsinger and Jeff Crawford for early data entry and programming and Drs. Sara Dobanny and Judah Rosenblatt for their earlier statistical analyses. Mary Sears, M.D. and other members of the Breast Cancer Task Force have been most helpful.

PARTICIPATING INVESTIGATORS

Frank M. Barry, M.D., Jack H. Berman, M.D., Masud R. Bhatti, M.D., Ronald Bukowski, M.D., A.M. Cooperman, M.D., Dale H. Cowan, M.D., Ludwig Doppisch, M.D., Robert L. Druet, M.D., Caldwell Esselstyn, M.D., Y.S. Fu, M.D., Carl Groppe, M.D., Vernon D. Hacker, M.D., John Horton, M.D., Ch.B., Harold B. Houser, M.D., Andrea Manni, M.D., Anna Rassiga, M.D., Ronald Reimer, M.D., Bruce A. Sabek, M.D., Ezra Steiger, M.D., Arthur A. Stein, M.D., J.E. Trujillo, M.D., Elden C. Weckesser, M.D., James K. Weick, M.D., and Robert W. Wroblewski, M.D.

REFERENCES

1. Allegra JC, Lippman ME: Estrogen receptor determination predicts response to tamoxifen therapy. Recent Results Cancer Res 71:16-9, 1980.
2. Beatson GT: On the treatment of inoperable cases of carcinoma of the mamma: suggestions for a new method of treatment with illustrative cases. Lancet 2:104-7, 162-5, 1896.
3. Bedx L, Pieters G, Smals A, Koenders A, Benraad T, Kloppenborg P: Tamoxifen versus ethinyl estradiol in the treatment of postmenopausal women with advanced breast cancer. Cancer Treat Rep 65:179-85, 1981.
4. Bonadonna G, Brusamolino E, Valagussa P, Rossi A, Brugnatelli L, Brambilla C, De Lena M, Tancini G, Bajetta E, Musumeci R, Veronesi U: Combination chemotherapy as an adjuvant treatment in operative breast cancer. N Engl J Med 294:405-10, 1976.
5. Bonadonna G, Rossi A, Valagussa P, Banfi A, Veronesi U: Adjuvant chemotherapy with CMF in breast cancer with positive axillary nodes In Salmon SE, Jones SE, editors: Adjuvant therapy of cancer, Amsterdam, 1977, North-Holland, pp 83-94.
6. Bonadonna G, Rossi A, Valagussa P, Banfi A, Veronesi U: The CMF program for operable breast cancer with positive axillary nodes: updated analysis on the disease-free interval, site of relapse and drug tolerance. Cancer 39:2904-15, 1977.
7. Bonadonna G, Valagussa P: Dose-response effect of adjuvant chemotherapy in breast cancer. N Engl J Med 304:10-15, 1981.
8. Breslow N: A generalized Kruskal-Wallis test for comparing K samples subject to unequal patterns of censorship. Biometrika 57:579-94, 1970.
9. Brodkey JS, Pearson OH: The case for hypophysectomy in breast cancer. In Morley TP, editor: Current controversies in neurosurgery. Philadelphia, 1976, Saunders, pp 321-6.
10. Buzdar AU, Powell KC, Blumenschein GR: Aminoglutethimide after tamoxifen therapy in advanced breast cancer: M.D. Anderson Hospital experience. Cancer Res 42:3448-50, 1982.

11. Clark GM, McGuire WL, Hubay CA, Pearson OH, Marshall JS, and participating investigators: Comparison of progesterone receptor with estrogen receptor in predicting disease-free survival in stage II breast cancer patients. (Abstract) Breast Cancer Research and Treatment 2:278, 1982.
12. Cocconi G, DeLisi V, Boni C, Mori P, Malacarne P, Amadori D, Giovanelli E: Chemotherapy versus combination of chemotherapy and endocrine therapy in advanced breast cancer. A prospective randomized study. Cancer 51:581-8, 1983.
13. Cooper RG, Holland JF, Glidewell O: Adjuvant chemotherapy of breast cancer. Cancer 44:793-98, 1979.
14. Crowe JP, Hubay CA, Pearson OH, Marshall JS, Rosenblatt J, Mansour EG, Harmann RE, Jones JC, Flynn WJ, McGuire WL, and participating investigators: Estrogen receptor status as a prognostic indicator for stage I breast cancer patients. Breast Cancer Res Treat 2:171-6, 1982.
15. Fabian C, Starnson L, El-Serafi M, Cain L, Hearne E: Clinical pharmacology of tamoxifen in patients with breast cancer: correlation with clinical data. Cancer 48:876-82, 1981.
16. Firusian N, Ohl S, Becher R: Results of tamoxifen therapy in patients with breast cancer. Recent Results Cancer Res 71: 142-5, 1980.
17. Fisher B: Biological and clinical considerations regarding the use of surgery and chemotherapy in the treatment of primary breast cancer. Cancer 40:574-87, 1977.
18. Fisher B, Carbone P, Economou SG, Frelick R, Glass A; Lerner H, Redmond C, Zelen M, Band P, Katrych DL, Wolmark N, Fisher ER, and other cooperating investigators: L-Phenylalaine mustard (L-Pam) in the management of primary breast cancer: a report of early findings. N Engl J Med 292:117-22, 1975.
19. Fisher B, Redmond C, Brown A, Wolmark N, Wittliff J, Fisher ER, Plotkin D, Bowman D, Sachs S, Wolter J, Frelick R, Desser R, LiCalzi N, Geggie P, Campbell T, Elias EG, Prager D, Koontz P, Volk H, Dimitrov N, Gardner B, Lerner H, Shibata H: Treatment of primary breast cancer with chemotherapy and tamoxifen. N Engl J Med 305:1-6, 1981.

20. Fisher B, Slack N, Katrych DL, Wolmark N: Ten year follow-up results of patients with carcinoma of the breast in a cooperative clinical trial evaluating surgical adjuvant chemotherapy. Surg Gynecol Obstet 140:528-34, 1975.
21. Gehan EA: A generalized Wilcoxon test for comparing arbitrarily singly-censored samples. Biometrika 52:203-23, 1965.
22. Gehan EA: Estimating survival functions from the life table. J Chronic Disease 21:629-44, 1969.
23. Glick JH, Creech RH, Torri S, Holroyde C, Brodovsky H, Catalano RB, Varano M: Tamoxifen plus sequential CMF chemotherapy versus tamoxifen alone in postmenopausal patients with advanced breast cancer: a randomized trial. Cancer 45: 735-41, 1980.
24. Goldhirsch A, Leuenberger U, Ryssel HW, Cavalli F, Sonntag RW, Joss RA, Brunner KW: Combination hormotherapy with tamoxifen and fluoxymesterone in patients with advanced breast cancer relapsing on hormonotherapy. Oncology 39:284-6, 1982.
25. Gross, AJ, Clark VA: Survival distributions: reliability applications. In Biomedical Sciences, NY, Wiley, 1975.
26. Harvey HA, Lipton A, White DS, Santen RJ, Boucher AE, Shafik AS, Dixon RJ and Members ofthe Central Pennsylvania Oncology Group: Cross-over comparison of tamoxifen and aminoglutethimide in advanced breast cancer. Cancer Res 42: 3451-3, 1982.
27. Hayward JL: The changing role of endocrine therapy in the management of advanced breast cancer. In Mouridsen HT, Palshof T, editors: Breast cancer - experimental and clinical aspects. Oxford, 1979, Pergamon, pp 81-2.
28. Hubay CA, Pearson OH, Marshall JS, Rhodes RS, Debanne SM, Mansour EG, Hermann RE, Jones JC, Flynn WJ, Eckert C, McGuire WL: Antiestrogen, cytotoxic chemotherapy, and Bacillus Calmette-Guerin vaccination in stage II breast cancer: a preliminary report. Surgery 87:494-501, 1980.
29. Hubay CA, Pearson OH, Marshall JS, Rhodes RS, Debanne SM, Mansour EG, Hermann RE, Jones JC, Flynn WJ, Eckert C, McGuire WL, and 27 participating investigators: Adjuvant chemotherapy, antiestrogen therapy and immunotherapy for stage II breast cancer. In Mouridsen HT, Palshof T (eds): Breast Cancer - Experimental and Clinical Aspects. Elmsford,

30. Hubay CA, Pearson OH, Marshall JS, Rhodes RS, Debanne SM, Rosenblatt J, Mansour EG, Hermann RE, Jones JC, Flynn WJ, Eckert C, McGuire WL, and 27 participating investigators: Adjuvant chemotherapy, antiestrogen therapy and immunotherapy for stage II breast cancer: 45 month follow-up of a prospective randomized clinical trial. Cancer (Suppl) 46:2805-8, 1980.

31. Hubay CA, Pearson OH, Marshall JS, Stellato TA, Rhodes RS, Debanne SM, Rosenblatt J, Mansour EG, Hermann RE, Jones JC, Flynn WJ, Eckert C, McGuire WL and 27 participating investigators: Adjuvant therapy of stage II breast cancer: 48 month follow-up of a prospective randomized clinical trial. Breast Cancer Res Treat 1:77-82, 1981.

32. Ingle JN, Ahmann DL, Green SJ, Edmonson JH, Creagan ET, Hahn RG, Rubin J: Randomized clinical trial of megestrol acetate versus tamoxifen in paramenopausal or castrated women with advanced breast cancer. Am J Clin Oncol 5:155-60, 1982.

33. Ingle JN, Green SJ, Ahmann DL, Edmonson JH, Nichols WC, Frytak S, Rubin J: Progress report on two clinical trials in women with advanced breast cancer. Trial I: Tamoxifen versus tamoxifen plus aminoglutethimide; Trial II: Aminoglutethimide in patients with prior tamoxifen exposure. Cancer Res 42:3461-7, 1982.

34. Jensen EV, Block GE, Smith S, Kyser K, DeSombre ER: Estrogen receptors and breast cancer response to adrenalectomy. Natl Cancer Inst Monogr 34:55-70, 1971.

35. Kiang DT, Frenning DH, Goldman AI, Ascensao VG, Kennedy BJ: Estrogen receptors and responses to chemotherapy and hormonal therapy in advanced breast cancer. N Engl J Med 299:1330-34, 1978.

36. Kiang DT, Frenning DH, Vosika GJ, Kennedy BJ: Comparison of tamoxifen and hypophysectomy in breast cancer treatment. Cancer 45:1322-5, 1980

37. Koenders AJM, Beex LVM, Geurts-Moespot J, Benraad TJ: Steroid hormone receptors in mammary carcinoma: the effect of tamoxifen. In Mouridsen HT, Palshof T, editors. Breast Cancer - experimental and clinical aspects. Oxford, 1979. Pergamon, pp 63-6.

38. Kolb R, Jakesz R, Rainer H: Results with tamoxifen in advanced mammary carcinoma. Recent Results Cancer Res 71: 146-8, 1980.

39. Lenzhafer R, Rainer N, Moser K, Jakesz R, Kolb R, Rainer G, Battelheim P, Morz R, Spona J, Bieglmayer C, Chaput B: Prognostic significance of estrogen receptors in breast cancer. In Salmon SE, Jones SE, editors: Adjuvant therapy of cancer III. New York, 1981, Grune & Stratton, pp 313-9.

40. Levin J, Markham MJ, Greenwald ES, Wollner D, Kream J, Zumoff B, Fukushima DK: Effect of tamoxifen treatment on cortisol metabolism and the course of the disease in advanced breast cancer. Cancer 47:1394-7, 1981.

41. Lippman ME, Allegra JC, Thompson EB, Simon R, Barlock A, Green L, Huff KK, Do HMT, Aitken SC, Warren R: The relation between estrogen receptors and response rate to cytotoxic chemotherapy in metastatic breast cancer. N Engl J Med 298: 1223-28, 1978.

42. Manni A, Arafah B, Pearson OH: Estrogen and progesterone receptors in the prediction of response of breast cancer to endocrine therapy. Cancer 46 (Suppl) 2838-41, 1980.

43. Manni A, Pearson OH: Antiestrogen-induced remissions in premenopausal women with stage IV breast cancer: effects on ovarian function. Cancer Treat Rep 64:779-85, 1980.

44. Meakin JW: Is there a place for adjuvant endocrine therapy of breast cancer? Recent Results Cancer Res 71:178-84, 1980.

45. Mouridsen HT, Palshof T, Rose C: Therapeutic effect of tamoxifen alone versus tamoxifen in combination with gestagen and oestrogen in advanced breast cancer. Recent Results Cancer Res 71:169-77, 1980.

46. Mouridsen HT, Palshof T, Engelsman E, Sylvester R: CMF versus CMF plus tamoxifen in advanced breast cancer in postmenopausal women. An EORTC trial. In Mouridsen HT, Palshof T, editors: Breast cancer - experimental and clinical aspects. Oxford, 1979, Pergamon, pp 119-23.

47. Mouridsen HT, Slaimtschik M, Dombernowsky P, Galshoj K, Palshof T, Rorth M, Doehnfeldt JL, Rose C: Therapeutic effect of tamoxifen versus combined tamoxifen and diethylstilboestrol in advanced breast cancer in postmenopausal women. In Mouridsen HT, Palshof T, editors: Breast cancer -

experimental and clinical aspects. Oxford, 1979, Pergamon, pp 107-10.

48. Palshof T: Symposium on the management of early breast cancer (stages I and II) Part II: Clinical experience with treatment methods. 5. Adjuvant endocrine therapy. Can J Surg 24: 379-84, 1981.

49. Palshof T, Mouridsen HT, Dachnfeldt JL: Adjuvant endocrine therapy of breast cancer - a controlled clinical trial of oestrogen and anti-oestrogen: preliminary results of the Copenhagen breast cancer trials. Recent Results Cancer Res 71:185-9, 1980.

50. Palshof T, Mouridsen HT, Dachnfeldt JL: Adjuvant endocrine therapy of primary operable breast cancer. Report on the Copenhagen breast cancer trials. In Mouridsen HT, Palshof T, editors: Breast cancer - experimental and clinical aspects. Oxford, 1979, Pergamon, pp 183-7.

51. Pannuti F, Martoni A, Fruet F, Strocchi E, DiMarco AR: Hormone therapy in advanced breast cancer: high dose medroxy-progesterone acetate (MAP) vs tamoxifen (TMX). Preliminary results. In Mouridsen HT, Palshof T, editors: Breast cancer - experimental and clinical aspects. Oxford, 1979, Pergamon, pp 93-8.

52. Patterson JS, Settatree RS, Adam HK, Kemp JV: Serum concentrations of tamoxifen and major metabolite during long-term nolvadex therapy, correlated with clinical response. In Mouridsen HT, Palshof T, editors: Breast cancer - experimental and clinical aspects. Oxford, 1979, Pergamon, pp 89-92.

53. Pearson OH, Hubay CA, Marshall JS, Gordon NH, McGuire WL, Mansour EG, Hermann RE, Jones JC, Flynn WJ, Eckert C and 24 participating investigators: Adjuvant endocrine therapy, cytotoxic chemotherapy in stage II breast cancer: five year results. Breast Cancer Res Treat (in press).

54. Pearson OH, McGuire WL, Brodkey J, Marshall J: Estrogen receptors and prediction of the response of metastatic breast cancer to hypophysectomy. In McGuire WL, Carbone PP, Vollmer EP, editors: Estrogen receptors in human breast cancer. New York, 1975, Raven Press, pp 31-6.

55. Pearson OH, Manni A, Arafah BM: Antiestrogen treatment of breast cancer: an overview. Cancer Res 42:3424-9, 1982.
56. Powles TJ, Gordon C, Coombes RC: Clinical trial of multiple endocrine therapy for metastatic and locally advanced breast cancer with tamoxifen-aminoglutethimide-danazol compared to tamoxifen used alone. Cancer Res 42:3458-60, 1982.
57. Preece PE, Wood RAB, Mackie CR, Cuschieri A: Tamoxifen as initial sole treatment of localized breast cancer in elderly women: a pilot study. Br Med J (Clin Res) 284:869-70, 1982.
58. Pritchard KI, Thomson DB, Myers RE, Sutherland DJ, Mobbs BG, Meakin JW: Tamoxifen therapy in premenopausal patients with metastatic breast cancer. Cancer Treat Rep 64:787-96, 1980.
59. Rose C, Thorpe SM, Lober J, Daanfeldt JL, Palshof T, Mouridsen HT: Therapeutic effect of tamoxifen related to estrogen receptor level. Recent Results Cancer Res 71:134-41, 1980.
60. Schein PS: The place of tamoxifen in the treatment of breast cancer. Recent Results Cancer Res 71:212-4, 1980.
61. Smith IE, Harris AL, Morgan M, Ford HT, Gazet JC, Harmer GL, White H, Parsons CA, Villardo A, Walsh G, McKinna JA: Tamoxifen versus aminoglutethimide in advanced breast carcinoma: a randomized cross-over trial. Br Med J (Clin Res) 283: 1432-4, 1981.
62. Steroid receptors in breast cancer. An NIH consensus development conference, Bethesda, Maryland, June 27-29, 1979. Cancer 46: (Suppl) 2759-62.
63. Stewart JF, Minton MJ, Rubens RD: Trial of tamoxifen at a dose of 40 mg. daily after disease progression during tamoxifen therapy at a dose of 20 mg. daily. Cancer Treat Rep 66:1445-6, 1982.
64. Stewart HJ, Forrest APM, Gunn JM, Hamilton T, Langlands AO, McFadyen IJ, Robert MM: The tamoxifen trial - a double-blind comparison with stilboestrol in postmenopausal women with advanced breast cancer. In Mouridsen HT, Palshof T (editors) Breast Cancer - Experimental and Clinical Aspects. Oxford, 1979, Pergamon, pp 83-8.

65. Stoll BA: Clinical experience with tamoxifen in advanced breast cancer. Recent Results Cancer Res 71:207-11, 1980.
66. Stoll BA: Recent developments in the endocrine treatment of breast cancer - experimental and clinical aspects. Oxford, 1979, Pergamon, pp 79-80.
67. Thomas DG, Breslow N, Gart JJ: Trend and homogeneity analysis of proportions and life table data. Comput Biomed Res 10: 373-81, 1977.
68. Tormey DC, Falkson G, Crowley J, Falkson HC, Voelkel J, Davis TE: Dibromodulcitol and adriamycin +/- tamoxifen in advanced breast cancer. Am J Clin Oncol 5:33-9, 1982.
69. Wada T, Koyama H, Terasawa T: Effect of tamoxifen in pre-menopausal Japanese women with advanced breast cancer (letter). Cancer Treat Rep 65:778-9, 1981.
70. Waseda N, Kato Y, Imura H, Kurata M: Effects of tamoxifen on estrogen and progesterone receptors in human breast cancer. Cancer Res 41:1984-8, 1981.
71. Westerberg H: Tamoxifen and fluoxymesterone in advanced breast cancer: a controlled clinical trial. Cancer Treat Rep 64: 117-21, 1980.

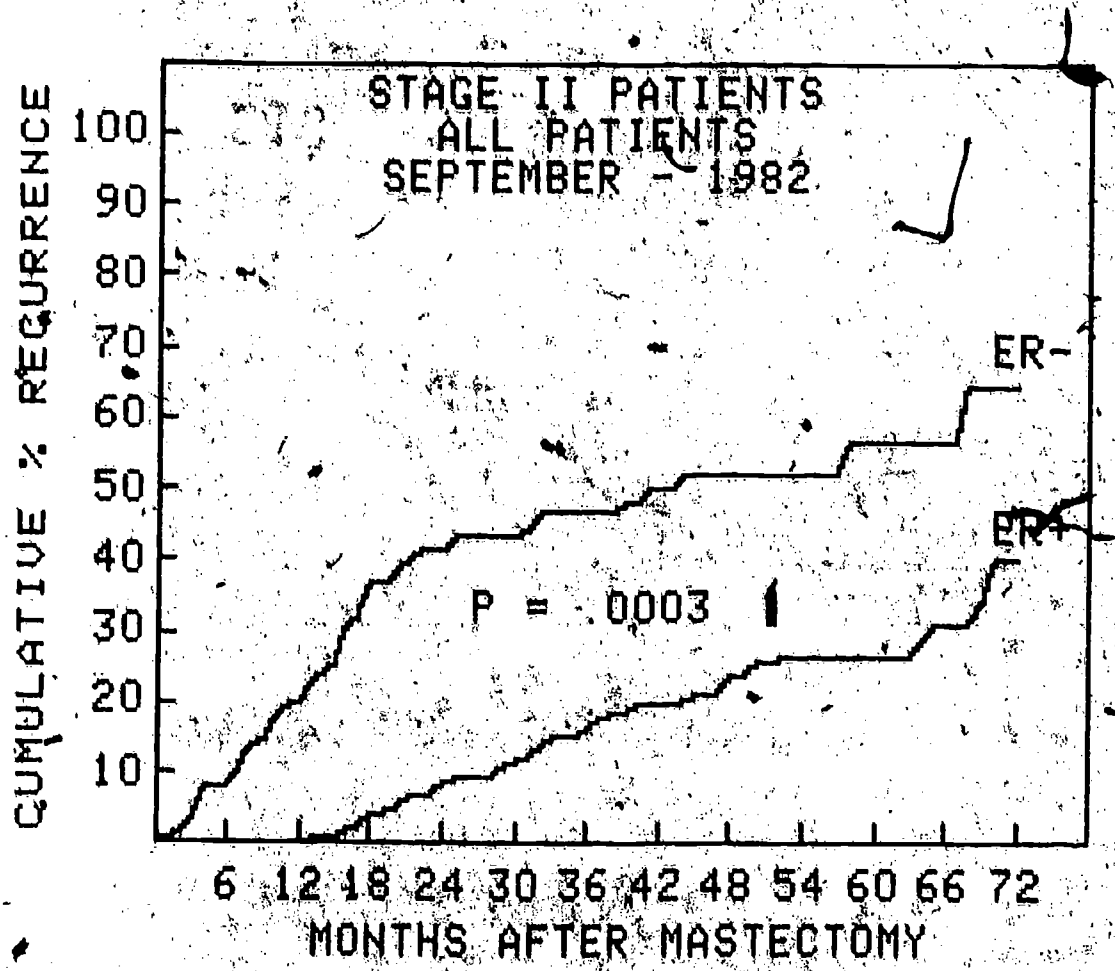

STAGE II PATIENTS
ALL PATIENTS
SEPTEMBER - 1982
CUMULATIVE % REGURRENCE
100
90
80
70
60
50
40
30
20
10
ER-
ER+
P = .0003
6 12 18 24 30 36 42 48 54 60 66 72
MONTHS AFTER MASTECTOMY

FIG. 1

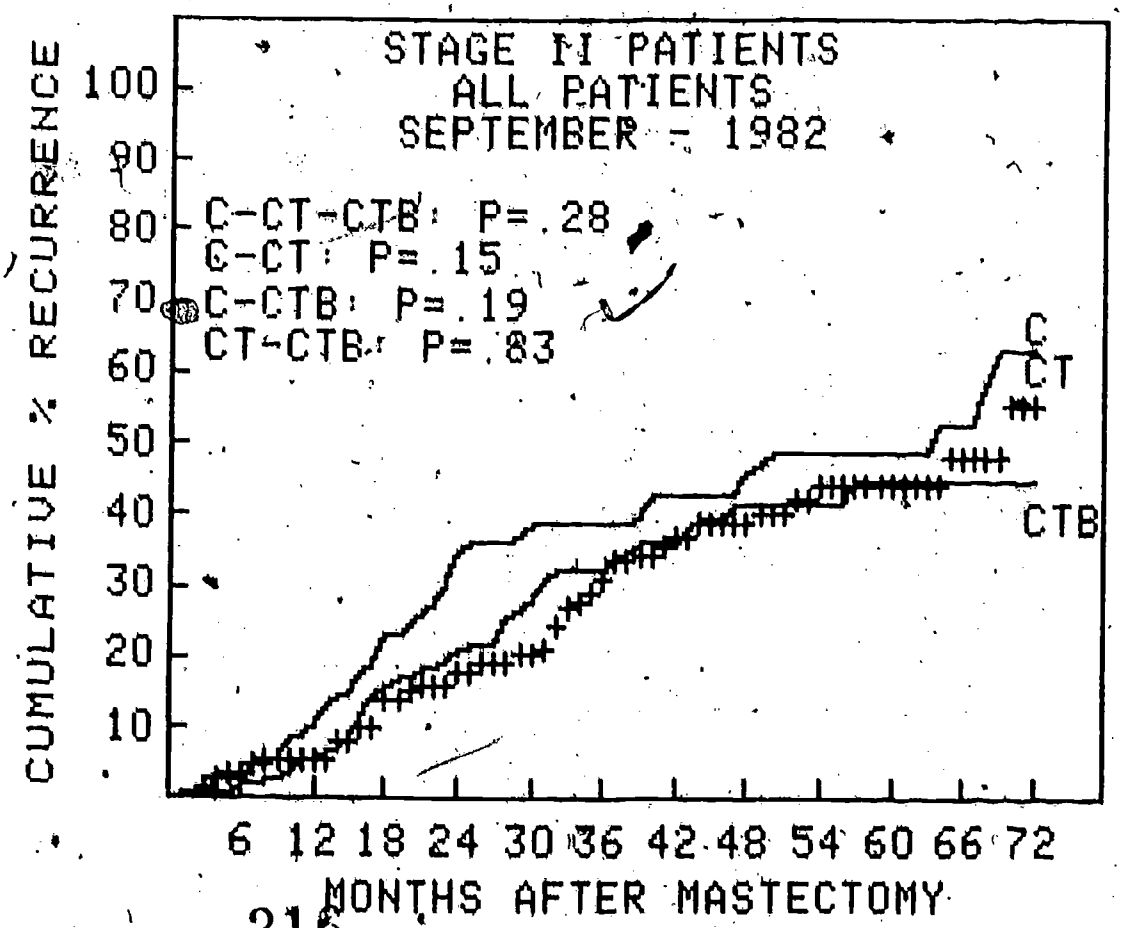

STAGE II PATIENTS
ALL PATIENTS
SEPTEMBER - 1982
C-CT-CTB: P=.28
C-CT: P=.15
C-CTB: P=.19
CT-CTB: P=.83
C
CT
CTB
CUMULATIVE % RECURRENCE
100
90
80
70
60
50
40
30
20
10
6 12 18 24 30 36 42 48 54 60 66 72
MONTHS AFTER MASTECTOMY

FIG. 2

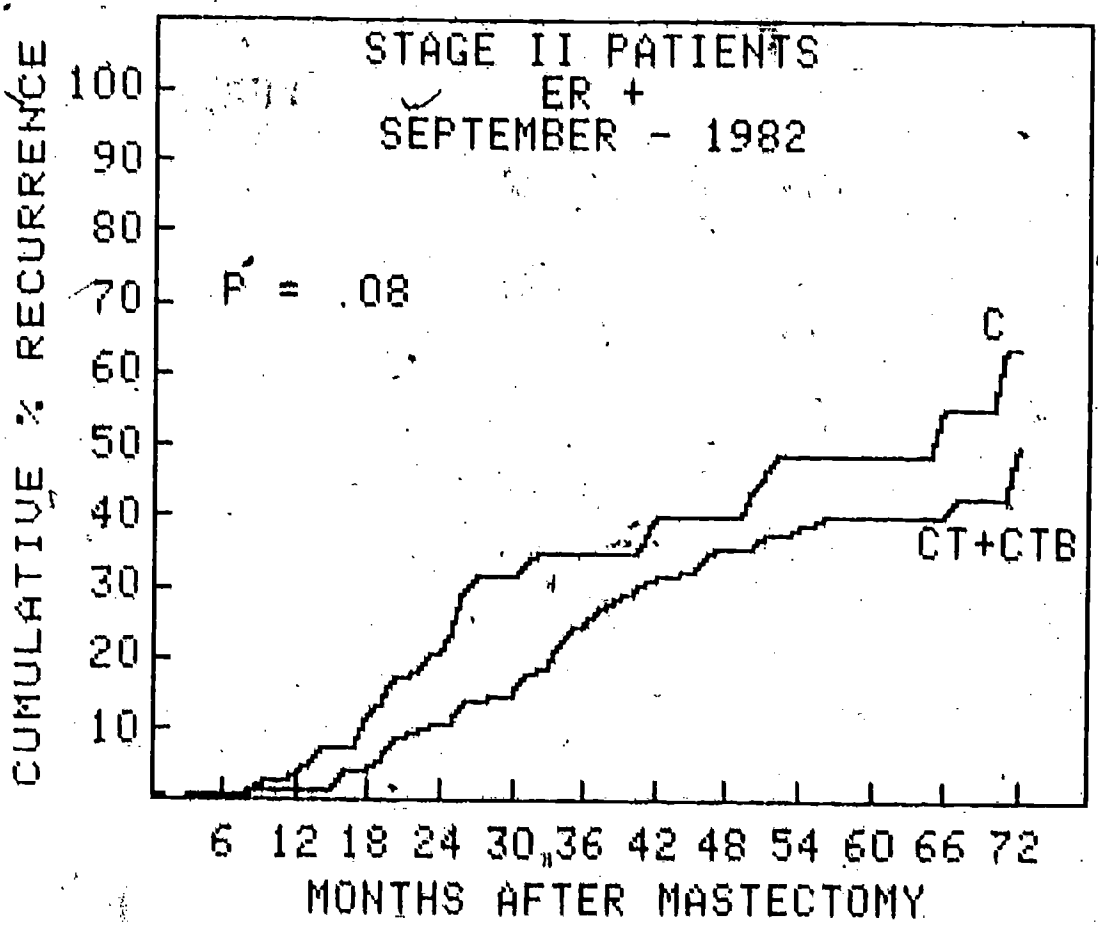

STAGE II PATIENTS
ER +
SEPTEMBER - 1982
P = .08
C
CT+CTB
CUMULATIVE % RECURRENCE
100
90
80
70
60
50
40
30
20
10
6 12 18 24 30 36 42 48 54 60 66 72
MONTHS AFTER MASTECTOMY

FIG. 3

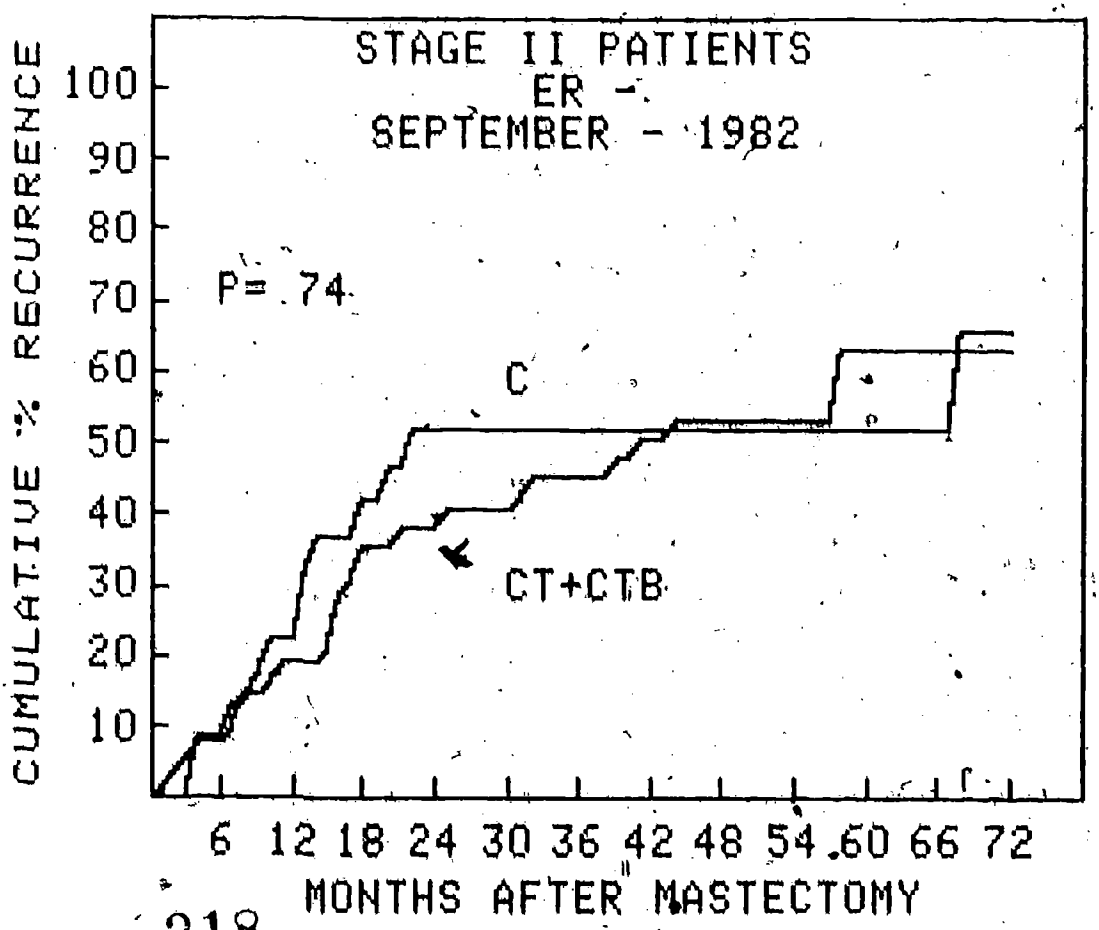

STAGE II PATIENTS
ER -
SEPTEMBER - 1982
P= .74
C
CT+CTB
CUMULATIVE % RECURRENCE
100
90
80
70
60
50
40
30
20
10
6 12 18 24 30 36 42 48 54 60 66 72
MONTHS AFTER MASTECTOMY

FIG. 4

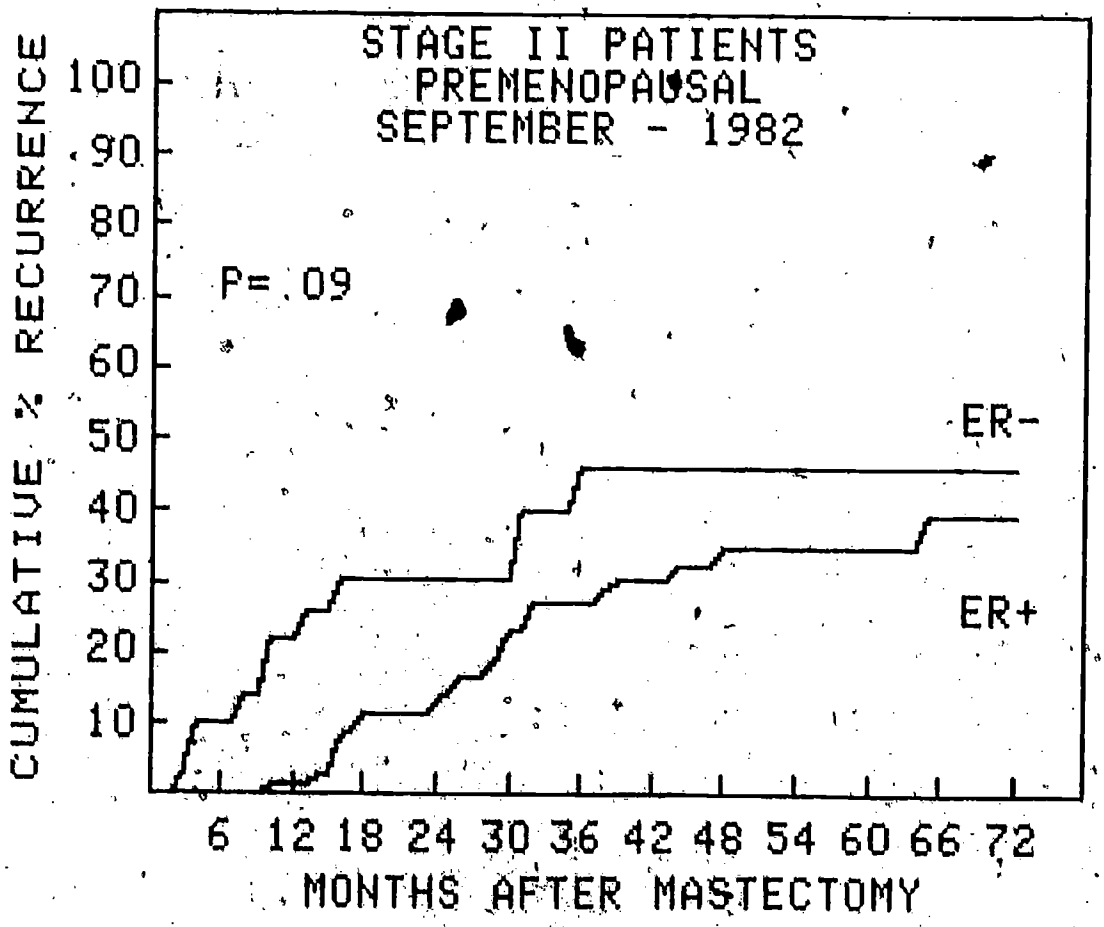
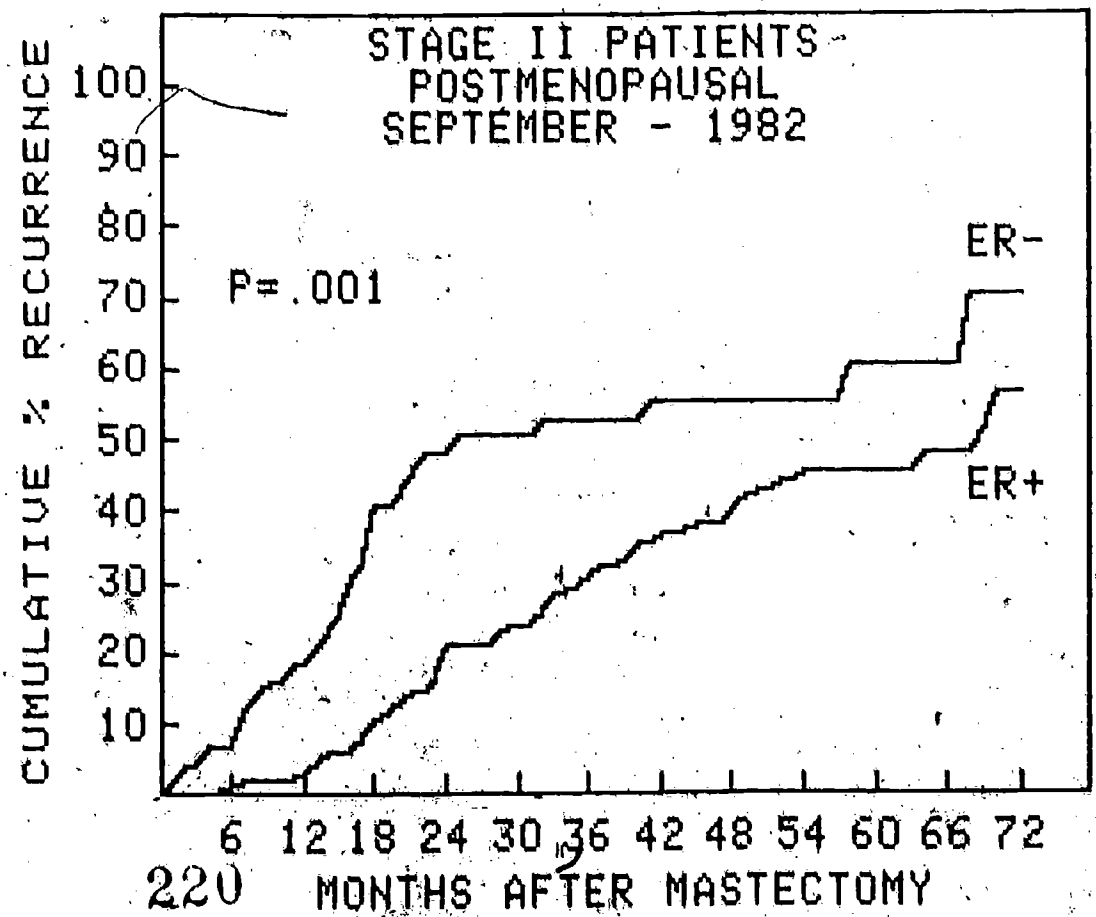

STAGE II PATIENTS
PREMENOPAUSAL
SEPTEMBER - 1982
P=.09
ER-
ER+
CUMULATIVE % RECURRENCE
100
90
80
70
60
50
40
30
20
10
6 12 18 24 30 36 42 48 54 60 66 72
MONTHS AFTER MASTECTOMY

FIG. 5

215


STAGE II PATIENTS
POSTMENOPAUSAL
SEPTEMBER - 1982
P=.001
ER-
ER+
CUMULATIVE % RECURRENCE
100
90
80
70
60
50
40
30
20
10
6 12 18 24 30 36 42 48 54 60 66 72
MONTHS AFTER MASTECTOMY

220

216

FIG. 6

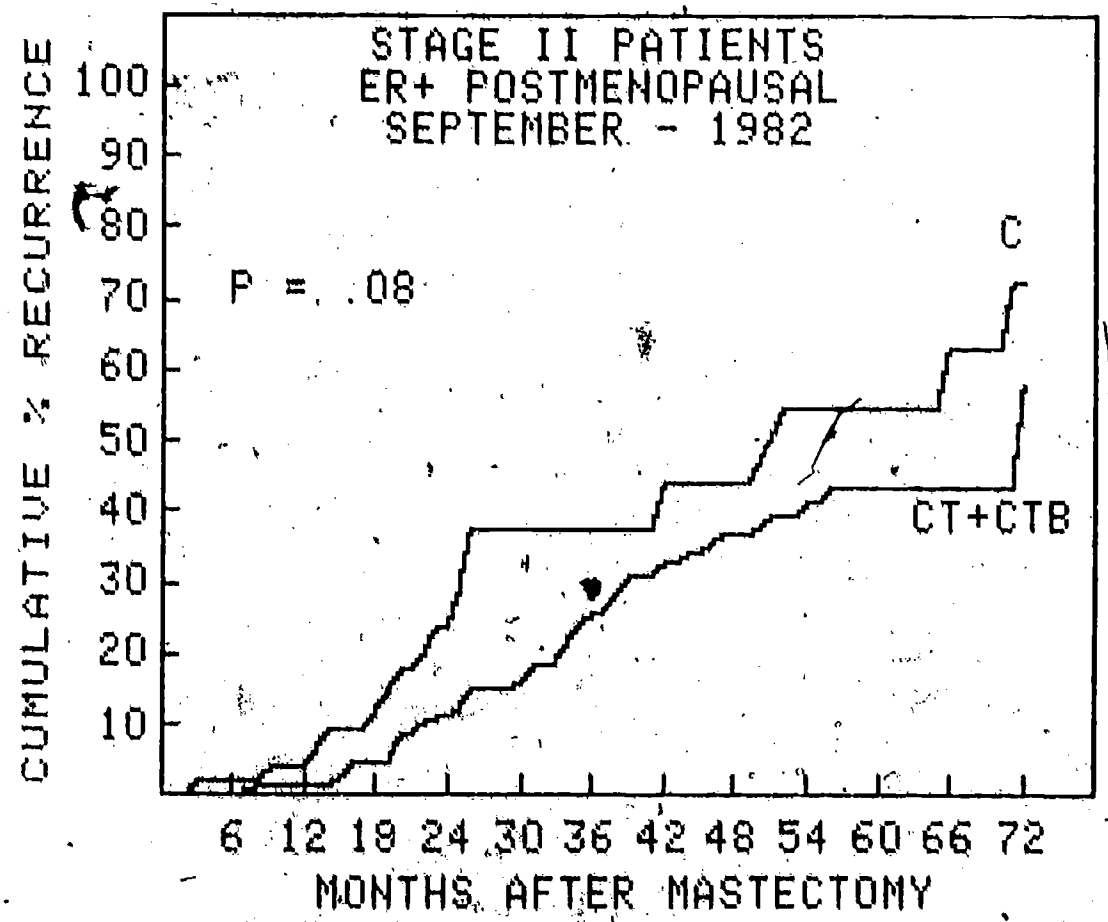
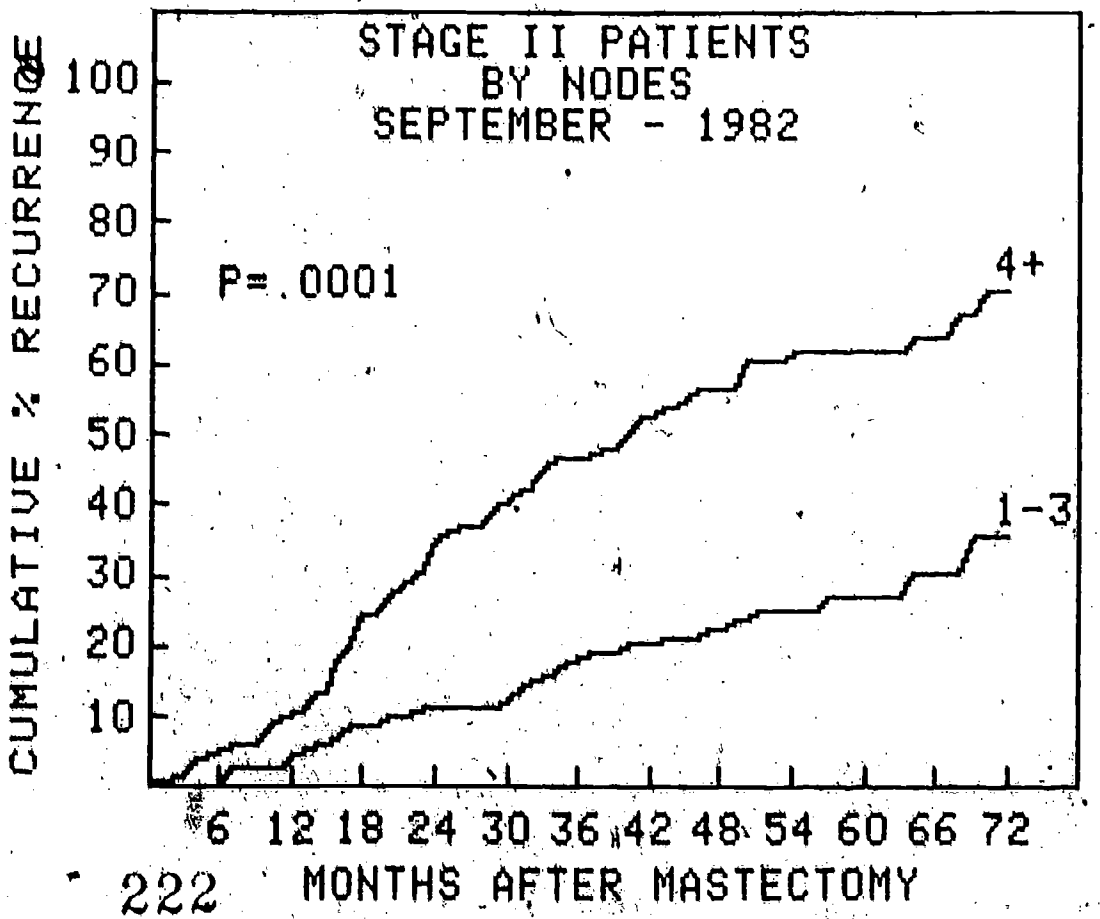

STAGE II PATIENTS
ER+ POSTMENOPAUSAL
SEPTEMBER - 1982
P = .08
C
CT+CTB
CUMULATIVE % RECURRENCE
100
90
80
70
60
50
40
30
20
10
6 12 18 24 30 36 42 48 54 60 66 72
MONTHS AFTER MASTECTOMY

FIG. 7


STAGE II PATIENTS
BY NODES
SEPTEMBER - 1982
P=.0001
4+
1-3
CUMULATIVE % RECURRENCE
100
90
80
70
60
50
40
30
20
10
6 12 18 24 30 36 42 48 54 60 66 72
MONTHS AFTER MASTECTOMY

222

218

FIG. 8

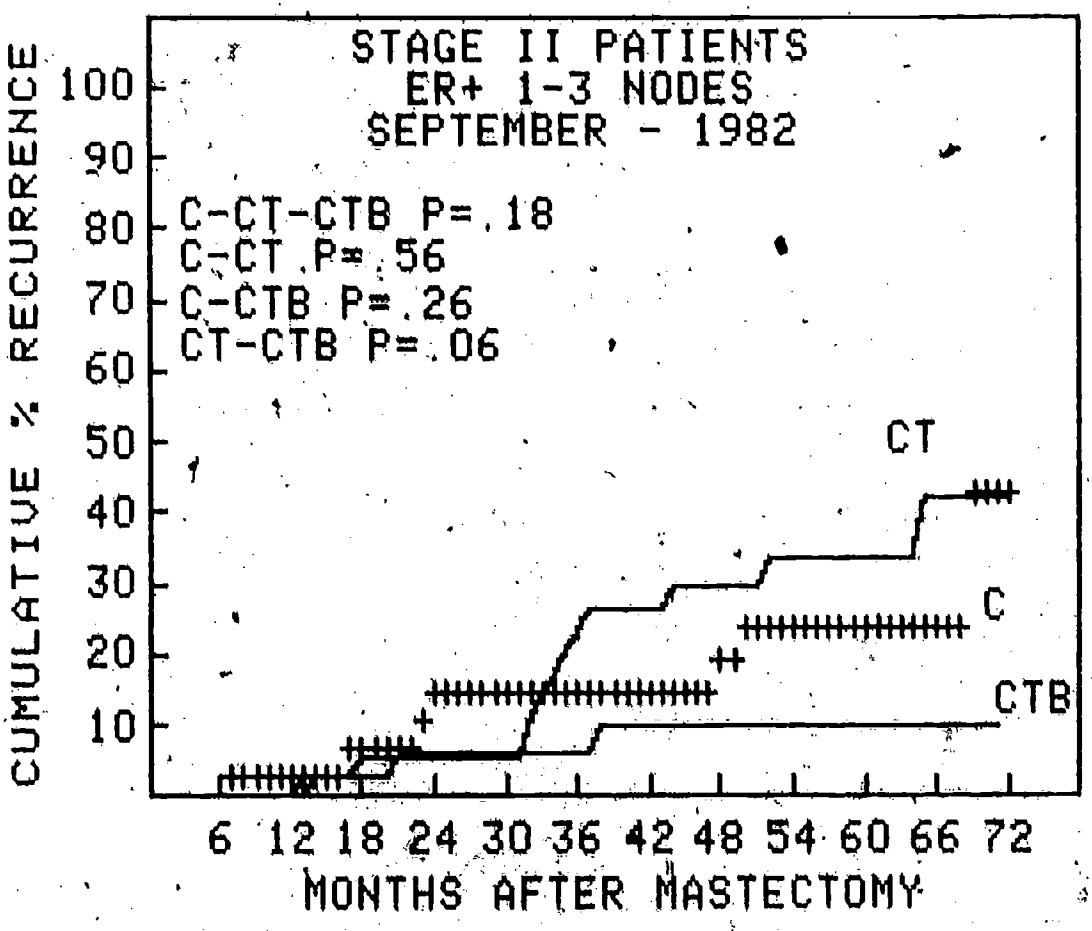

STAGE II PATIENTS
ER+ 1-3 NODES
SEPTEMBER - 1982
C-CT-CTB P=.18
C-CT P=.56
C-CTB P=.26
CT-CTB P=.06
CUMULATIVE % RECURRENCE
100
90
80
70
60
50
40
30
20
10
CT
C
CTB
6 12 18 24 30 36 42 48 54 60 66 72
MONTHS AFTER MASTECTOMY

FIG. 9

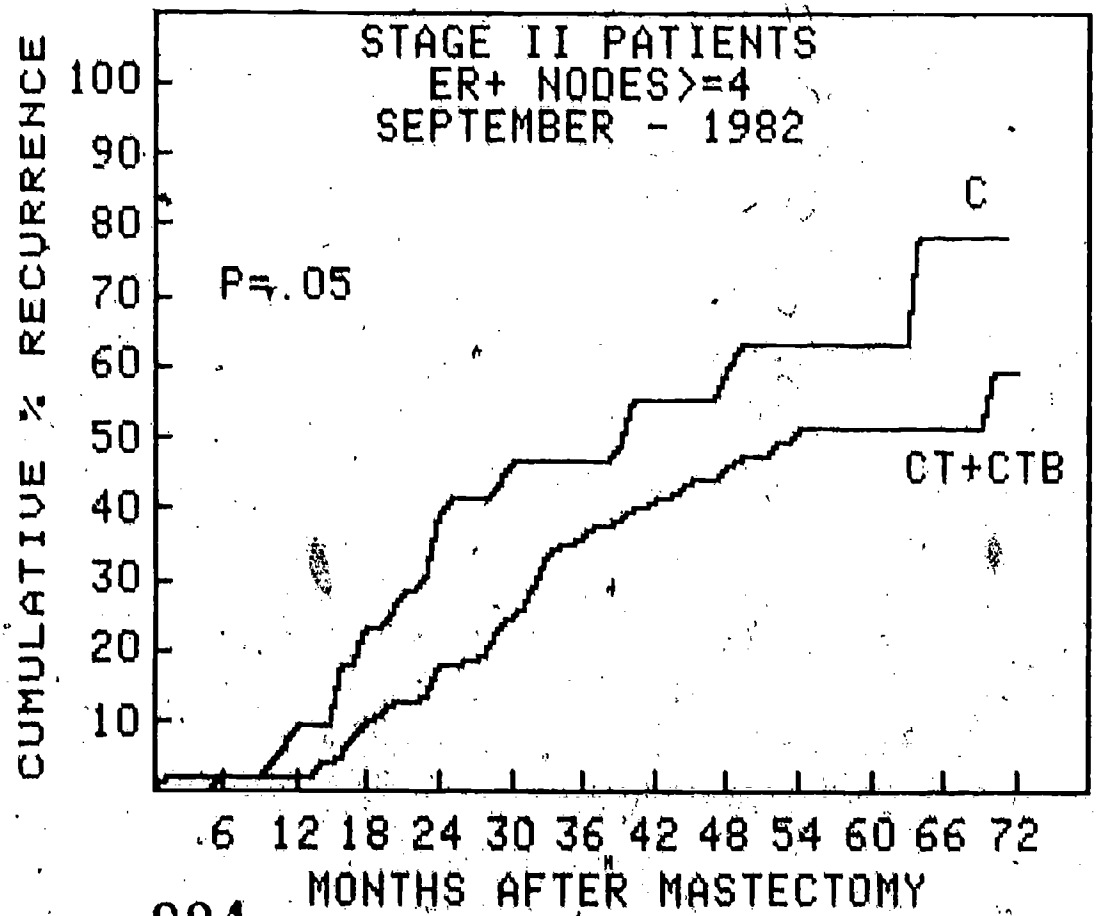

STAGE II PATIENTS
ER+ NODES>=4
SEPTEMBER - 1982
C
P=.05
CT+CTB
CUMULATIVE % RECURRENCE
100
90
80
70
60
50
40
30
20
10
6 12 18 24 30 36 42 48 54 60 66 72
MONTHS AFTER MASTECTOMY

FIG. 10

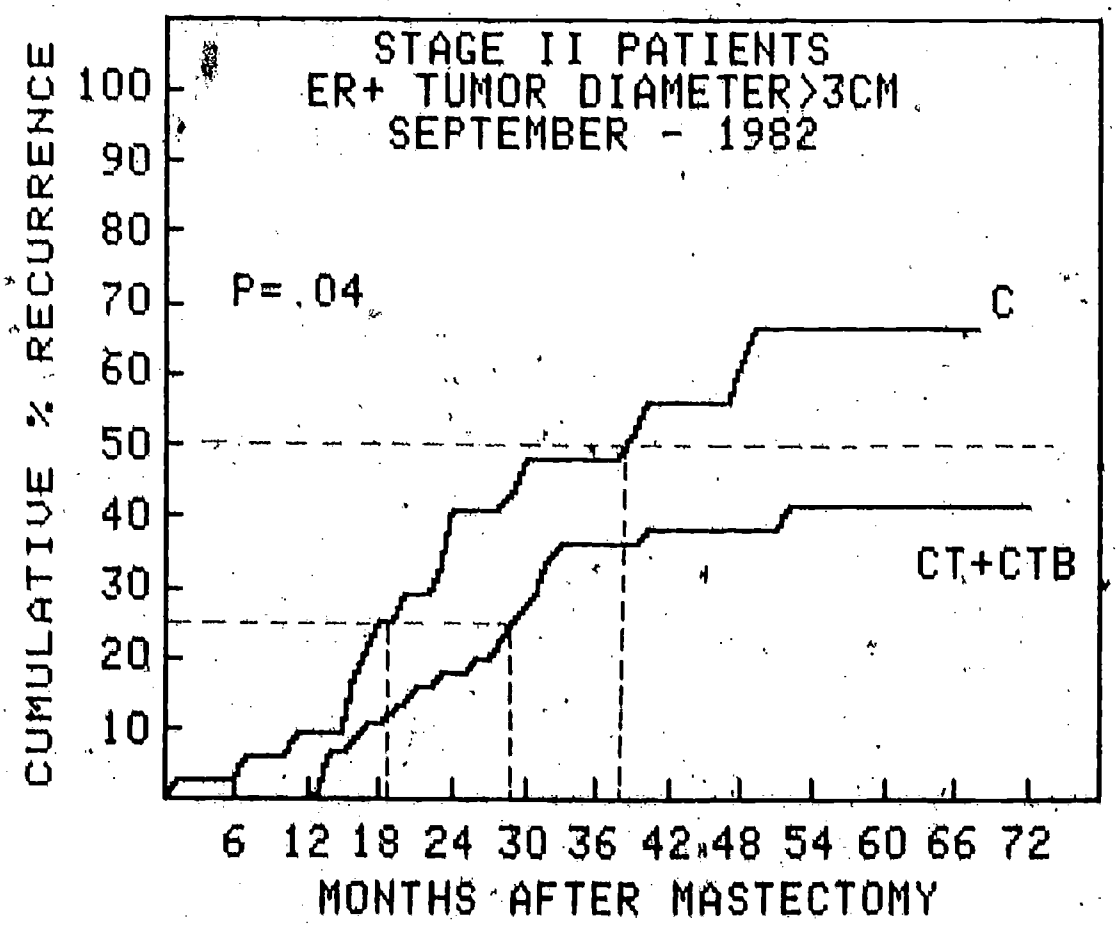
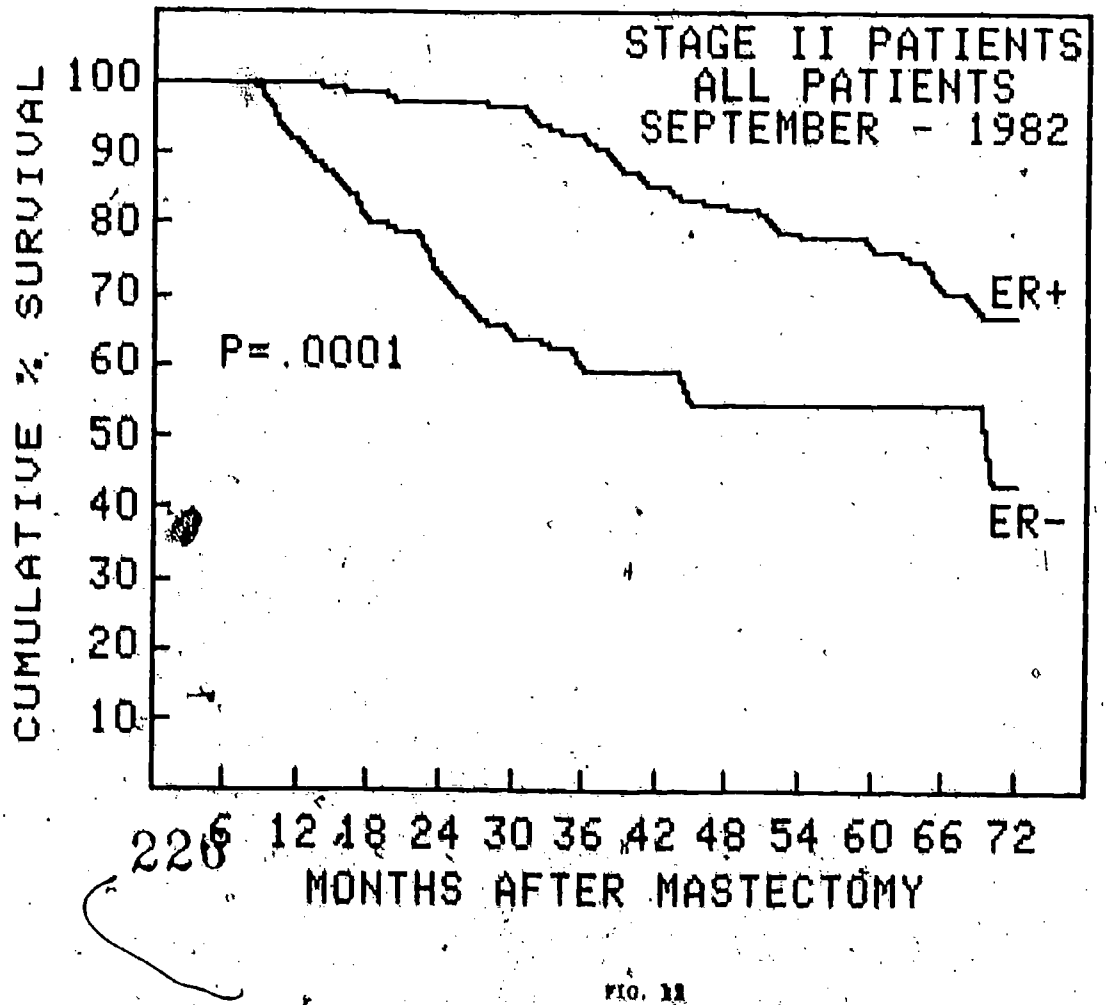

STAGE II PATIENTS
ER+ TUMOR DIAMETER>3CM
SEPTEMBER - 1982
P=.04
C
CT+CTB
CUMULATIVE % RECURRENCE
100
90
80
70
60
50
40
30
20
10
6 12 18 24 30 36 42 48 54 60 66 72
MONTHS AFTER MASTECTOMY

FIG. 11


STAGE II PATIENTS
ALL PATIENTS
SEPTEMBER - 1982
CUMULATIVE % SURVIVAL
100
90
80
70
60
50
40
30
20
10
P=.0001
ER+
ER-
6 12 18 24 30 36 42 48 54 60 66 72
MONTHS AFTER MASTECTOMY

226

FIG. 11

HORMONE RECEPTORS - AN UPDATE AND APPLICATION

Charles A. Hubay, M.D., Bahaddin Arafah, M.D., Nahida H. Gordon, Ph.D.,
Sigrid P. Guyton, M.D., Joseph P. Crowe, M.D. and Participating Investigators*

From the Departments of Surgery, Mathematics and Medicine, Case Western Reserve University, University Hospitals of Cleveland and Participating Institutions**

Supported by Public Health Service Contracts CB-23922 (Formerly CB-43990) (CAH) and CB-23862 (WLM) from the National Cancer Institutes of Health, Bethesda, Maryland and Clark Dunlap Fund (University Hospitals of Cleveland, Cleveland, Ohio)

Address for reprints: Charles A. Hubay, M.D.
2074 Abington Road
Cleveland, Ohio 44106

216/844-3024 (O)
216/831-1594 (H)

INSTITUTION**	PARTICIPATING INVESTIGATORS*
Albany Medical College, Albany, NY	Charles Eckart, M.D. John Horton, M.D., CM.B. Arthur S. Stein, M.D.
Albany Regional Cancer Center, Albany, NY	Robert W. Sponzo, M.D.
Akron General Medical Center, Akron, OH	Douglas Evans, M.D. Robert W. Wroblewski, M.D.
Cleveland Clinic Foundation, Cleveland, OH	Ronald Bukowski, M.D. A.M. Cooperman, M.D. Caldwell Esselstyn, M.D. Carl Groppe, M.D. Robert E. Hermann, M.D. Ronald Reimer, M.D. Bruce Sabek, M.D. Ezra Steiger, M.D. James C. Weick, M.D.
Cleveland Metropolitan General Hospital, Cleveland, OH	Edward G. Mansour, M.D.
Euclid General Hospital, Cleveland, OH	Vernon D. Hacker, M.D.
Olean Medical Group, Olean, NY	Frances M. Bohan, M.D. Robert Krall, M.D. Harry L. Lochte, M.D.
St. Elizabeth Hospital, Youngstown, OH	Sudershan K. Garg, M.D. F.C. Kocab, M.D. Stephen Ondash, M.D.

INSTITUTION	PARTICIPATING INVESTIGATORS
St. Luke's Hospital, Cleveland, OH	Jack H. Berman, M.D.
	Dale H. Cowan, M.D.
	James C. Jones, M.D.
	Anne L. Rassiga, M.D.
University Hospitals of Cleveland, Cleveland, OH	Frank M. Barry, M.D.
	Robert L. Druet, M.D.
	Yao S. Fu, M.D.
	Andrea Manni, M.D.
	James S. Marshall, M.D.
	Geoffrey Mendelsohn, M.D.
	Olof H. Pearson, M.D.
	J.E. Trujillo, M.D.
	Elden C. Weckesser, M.D.
University of Texas, San Antonio, TX	Gary Clark, Ph.D.
	Minerva De La Garza
	William L. McGuire, M.D.
Youngstown Hospital Association, Youngstown, OH	Masud R. Bhatti, M.D.
	Ludwig Deppisch, M.D.
	William J. Flynn, M.D.
	Renwick Goldberg, M.D.
	Lawrence Pass, M.D.

ACKNOWLEDGEMENTS

The authors thank all other surgeons whose patients were entered into this collaborative study. We also thank the following nurse clinicians: Rody Brodhead, Catherine Damm, Lib Fisher, Robin France, Ginny Gibbons, Ethel Gary, Ina Hardesty, Belva Hardin, Norma Jarmusch, Mary Ann Ladigo, Marjorie Naughton, Marge Norder, Angela Sheehan, Michele Trombly, Nancy Urbancic and Roxie Wolfe. We thank Jane Brumberg, the Administrative Coordinator; Bertha J. Adams and Theresa Courtland for secretarial assistance. Our thanks to the following data managers: Linda Bonacquisti, Barbara Demyan and Noreen Kadlowec. Dr. Mary E. Sears and other members of the Breast Cancer Task Force have been most helpful.

We will be forever grateful to the brave women volunteering for these studies. Most became boosters of the the programs and were helpful in allaying the fears and anxieties of women hesitant to accept randomized therapy. Their courage and confidence is inspiring to all.

HORMONE RECEPTORS - AN UPDATE AND APPLICATION

The first established usefulness of alterations of human sex steroid hormones in breast cancer was published by Beatson in 1896 (2). Beatson did his first oophorectomy for disseminated breast cancer on June 15, 1895 and noted that in one patient "all vestige of the previous cancerous disease had disappeared postoperatively at eight months". Thus, the hormone dependency of human breast cancer was established nearly a hundred years ago. It is now well known that one third of women with breast cancers will benefit following hormonal manipulation. Estrogen and other hormones have been implicated in the growth of breast cancer cells in humans and in experimental animal models. The source of estrogen in premenopausal women is primarily the ovary (See Fig. 1). However, following the menopause, (Fig. 2), conversion of adrenal androgens by aromatization in several peripheral sites, notably fat and muscle, provides the major source of circulating levels of estrone and estradiol. Endocrine therapy for advanced breast cancer can be ablative (oophorectomy, hypophysectomy, adrenalectomy) or additive (progestins, androgens, estrogens). The introduction of antiestrogen therapy (Nolvadex, tamoxifen citrate) has provided an important advance in the management of hormone-dependent breast cancer due to its effectiveness and its relative lack of side effects. Thus, hormonal control of significant numbers of breast cancers are possible in advanced disease, but the use of these compounds in early stages of the disease are not as yet well established.

The introduction of measurement of hormone receptors in tumor specimens over the past decade provided a major advance in the selection of patients likely to have hormone dependent cancers. In 1971, Jensen (16) first reported on the usefulness of measuring estrogen receptors (ER) in tumor specimens for predicting the response to surgical adrenalectomy. Jensen's findings have been subsequently confirmed by many investigators over the past decade. It is now well established

that approximately 60% of women with advanced ER positive tumors will respond to ablative or additive endocrine treatments. In contrast, the response in women with ER negative tumors is less than 10%. It is clear, however, that the presence of ER in a tumor does not guarantee hormone dependency of that tumor since 35 to 40% of women with ER positive tumors do not respond to endocrine treatments. A possible explanation (23) may be that certain breast cancers retain the ability to bind estradiol, but may be unable to proceed with the subsequent steps of estrogen action, such as migration of the estrogen-estrogen receptor complex into the nucleus of cancer cells, with subsequent stimulation of mRNA and initiation of mitogenesis. Thus, certain breast cancers can have estrogen receptors, but may be hormone independent.

Numerous studies over the past decade have demonstrated the presence of other hormone receptors (such as progesterone and prolactin) in human breast cancer cells. It is now known that the synthesis of progesterone receptor (PgR) is a product of estrogen action on cells, i.e., it is an estrogen dependent process. It would therefore be reasonable to assume that tumors containing both ER and PgR are more likely to be hormone dependent than those containing ER alone. In fact, this assumption proved to be true (22). The presence of both hormone receptors in a tumor (ER and PgR) is a better predictor of response to endocrine treatments. The likelihood of this response is approximately 75-80%, whereas it is only 60% for ER positive tumors.

Hubay and colleagues (11-15) in their long term clinical trial on women with Stage I and II operable breast cancer have shown that women with breast neoplasms having estrogen receptors have a significantly longer disease-free survival and overall <u>total</u> survival than those women whose tumors lacked estrogen receptors. More recently, analysis of the PgR data in these patients revealed that the PgR level in the primary tumor is an important predictor of disease

free survival (4). It should be emphasized that human breast cancer appears to be not an "all or nothing" condition but a spectrum of disease. Thus, because of the important therapeutic and prognostic implications of the receptor status, biochemical measurements of receptors should be performed for every patient with a primary breast cancer and for any patient with recurrent disease where tumor-biopsy assay is feasible.

Although the biochemical measurements of receptors are technically demanding, Oxley (30) has recently reviewed the analytic accuracy of breast cancer estrogen and progesterone receptor assays using various laboratories and found a 90-95% concurrence. McCarty (20) compared histochemical methods for ER localization and quantitation with established biochemical methods. It was noted that the predictive value for clinical response was highest in the biochemical assay and concluded that histochemical assays do not correlate accurately with clinical response.

MATERIAL AND METHODS

Beginning in 1974, we began a prospective randomized, multi-institutional clinical trial to study the effect of adjuvant therapy on surgically treated Stage II breast cancer patients. Chemotherapy (CMF), antiestrogen therapy (Nolvadex) and Bacillus Calmette-Guerin (BCG) immunotherapy were utilized in the trial. This was the first study in which patient stratification was based on the presence or absence of estrogen receptors in the primary tumors. The details of this clinical treatment program have been previously published (11-15) along with the five and six year results (15,31).

In this study which concluded in 1979, long-term follow-up has shown that the addition of Nolvadex to CMF adjuvant therapy significantly delayed recurrence in Stage II patients particularly those with positive estrogen receptors regardless of menopausal status. This delay in recurrence was more pronounced in ER+ patients

with 4 or more positive nodes and ER+ patients who are postmenopausal. Overall survival was highly significantly prolonged in ER+ patients when compared to ER- patients. A recent analysis of a subset of these patients (N=189) by Clark, et al (4), demonstrated improved recurrence-free survival and total survival when progesterone receptor levels were elevated.

In addition to the 311 Stage II breast cancer patients entered in this randomized trial, 507 Stage I, node negative patients who were treated solely by modified radical mastectomy were similiarly followed. Estrogen receptor assays of the primary tumors of these patients were performed in one laboratory (Wm. L. McGuire) to insure uniformity of measurements. Recurrence, survival and clinical data was collected for these patients. Crowe (9,10) has recently published findings (with a median follow-up of 51 months) for the Stage I patients and has pointed out the prognostic importance of ER levels in this group.

The recurrence-free survival distributions obtained by the Kaplan-Meir product limit method for 507 Stage I patients up to 84 months show a significant difference in recurrence between the ER+ and ER- groups (Fig 3), with the latter recurring at an increased rate. There are no differences in patient clinical characteristics between the two groups. Figure 4 shows the recurrence-free survival distribution of two groups of Stage I patients; the first group are those patients with tumors greater than 2 cm in diameter and the second group are those with tumors less than 2 cm in diameter. A comparison of the disease-free survival distributions of these patients fails to show a significant difference, probably due to the overriding effect of absent nodal involvement. The recurrence-free survival distributions of the premenopausal ER+ and ER- patients (Fig. 5) are very similiar. This may reflect continued estrogen effect in this group. On the other hand, the recurrence-free distribution of postmenopausal ER+ and ER- patients (Fig. 6) reveal a marked increase in recurrence for the

ER- group. Figure 7 depicts the overall survival distributions of the ER+ and ER- Stage I patients up to 84 months. Note the 90% survival for ER+ patients.

From these data, we have concluded that in Stage I breast cancer, total mastectomy and axillary dissection is an effective form of therapy and that estrogen receptor measurement is helpful in providing prognostic information in subsets of this group. Furthermore, hormone receptor measurement may be of help in the design of further therapy for those patients showing earlier recurrence patterns.

From our observations in Stage II patients where recurrence seemed to accelerate following cessation (at 12 months) of adjuvant Nolvadex therapy, we postulated that more prolonged antiestrogen treatment might be of further benefit. To test this hypothesis, adjuvant Nolvadex treatment was extended to 36 months for all ER+ patients.

Our Beta trial outlined in Figs. 8,9,10 was undertaken for both ER+ and ER- pre and postmenopausal Stage II-III patients. Since three drug chemotherapy (CMF) seemed to be of little benefit for the previously studied ER- groups, it seemed reasonable to switch to the more effective 5-drug (CMFVP) chemotherapy, CMFVP has been shown by Cooper (8) and Knight, et al (18) to be a more effective therapy for node positive patients. The latter's prospective randomized trial comparing CMFVP and L-Pam, showed clear-cut advantage for the more intensive 5-drug regimen.

Weiss, et al (36) have recently reported results of the CALGB study comparing CMF vs 5-drug (CMFVP) therapy in comparable groups of breast cancer patients with more than 3 involved axillary lymph nodes. Here, CMFVP was significantly superior to CMF treatment. The toxicity and side effects were noted to be tolerable and nearly identical to CMF. Unfortunately, knowledge of hormone receptor status is not available for these patients.

The Beta clinical trial is as yet new and has small numbers of patients (Table I). As seen in Fig. 8, premenopausal women having ER+ tumors underwent

surgical oophorectomy following modified radical mastectomy. They were then randomized to Nolvadex (20 mg bid) for 3 years (O+T) or 5-drug chemotherapy for one year post operative along with Nolvadex (20 mg bid) daily for one year and then Nolvadex (20 mg bid) alone for two subsequent years (O+T+5D). The ER+ postmenopausal patients (Fig. 9), were not subjected to any further surgery following mastectomy, but similarly randomized to Nolvadex alone for three years (T) or to the combined endocrine-chemotherapy (T+5D) as outlined. The ER- patients (Fig.10), both pre and postmenopausal, received one year of adjuvant 5-drug chemotherapy.

All patients were followed and had physical examinations at specified intervals. Participating patients received follow-up mammography, chest x-rays and bone scans at yearly intervals, in an attempt to detect both clinical and occult recurrence. If clinical recurrence was suspected or detected at anytime, appropriate x-rays or scans, along with biochemical testing was initiated.

Results to March 1984 for this clinical trial (Beta) are shown in Figs. 11 to 15. The investigators emphasize that the results are preliminary. Figure 11 compares oophorectomy and Nolvadex (O+T) therapy with combined chemo-endocrine treatment (OT+5D) in premenopausal patients. As is seen, one of eighteen O+T patients has recurred to date. That recurrence at 41 months, which was five months following cessation of Nolvadex treatment, reinforces our observation that recurrence accelerated in the Alpha study when Nolvadex was withheld following 12 months therapy. Owing to the small number of patients and short followup, the value of addition of chemotherapy cannot be evaluated at the present time.

Comparison of recurrence between Alpha and Beta ER+ premenopausal patients is shown in Fig. 12. Oophorectomy plus Nolvadex patients, with or without chemotherapy, appear to have delayed recurrence. Figure 13 shows comparison of Nolvadex alone (T) and Nolvadex+5-drug (T+5) therapy in postmenopausal patients. Larger

number of patients in each group lend credence to findings to date that the addition of chemotherapy delays recurrence, although this difference is not as yet significant.

Figure 14 depicts the recurrence distributions for all ER+ patients. Larger numbers (58 vs 48) of patients appears to demonstrate that, at the present follow-up, the evidence for additional 5-drug chemotherapy being helpful is not overwhelming. Figure 15 compares cumulative recurrence distribution for both ER- and ER+ Stage II patients. No significant difference is noted between groups in marked contrast with Alpha patients. This may suggest therefore, that chemotherapy with 5-drugs appears to be helpful in delaying recurrence in ER- patients. Total numbers are as yet small and careful, prolonged follow-up is needed before any solid conclusions can be made.

DISCUSSION

Endocrine treatment was the first systemic adjuvant therapy to be used in women with operable breast cancer. The aim was to improve disease-free survival in such patients. The first prospective randomized studies utilized radiation castration by Cole and her colleagues (6,7) in Manchester, England. Ovarian irradiation resulted in an increase in disease-free survival in both Stage I and II breast cancer. Crude survival was also increased. Unfortunately, estrogen receptors were not being measured at the time of her study.

Nissen-Meyer of Norway (28) had previously studied a highly selected group of premenopausal women with breast cancer and showed that disease-free survival in the castrated women was significantly longer than women not similarly castrated. In a 1975 update on the randomized prophylactic ovarian irradiation groups (29), he showed significantly prolonged disease free survival, i.e., delayed recurrence. Crude survival differences, however, though slightly benefiting the irrradiated groups in Stage I and Stage II disease, were not statistically significant

at 15 years follow-up.

Meakin and co-workers (24,25,26) combined radiation castration and long-term prednisone therapy to suppress adrenal hormone secretion. Follow-up at 10 years showed an advantage for both disease-free survival and total survival in the combined group. Surgical ablative therapy of ovarian function was similarly studied by Ravdin, et al (35). In this controlled prospective randomized clinical trial, they failed to demonstrate that prophylactic oophorectomy was beneficial for disease-free survival or total survival during the first 36 months postoperatively. Follow-up of these patients was too short, however, to demonstrate effectiveness. More recently, Bryant and Weir (3) reported that surgical castration significantly improved both disease-free and total survival in Stage I and II breast cancer after 10 years of follow-up. Thus, it seems that ovarian ablation, by providing estrogen deprivation in premenopausal women with operable breast cancer, can result in significantly prolonged disease free survival. Discriminant selection of patients by receptor analysis, however, is mandatory.

The antiestrogen drugs, Nafoxidine and Nolvadex, have been shown to influence favorably the therapy of metastatic or Stage IV breast cancer patients (21,27,32,33,34). With the advent of such new therapies, the number of clinical trials have mushroomed. Although final results are as yet pending in most, the use of antiestrogens have been enthusiastically embraced and are widespread in clinical practice.

In our studies, extensive use has been made of both estrogen and progesterone receptor measurement not only for choice of treatment but also for providing prognostic information. Endocrine adjuvant treatment for ER+ breast cancers, both in pre and postmenopausal women has been shown to be effective and worthwhile. Clark, et al (4) have recently presented evidence that not only did the presence, but the absolute level of progesterone receptors in breast cancer tissue, are

powerful predictors of disease-free survival (Fig. 16,17), whereas levels of estrogen receptors appear less so (Fig 18). It is imperative, however, that whenever possible, both estrogen and progesterone receptors be measured quantitatively on tumor tissue from all breast cancer patients.

The authors emphasize that early detection and therapy of breast cancer offers the best chance of "cure". We believe that in Stage I patients (earlier disease), until matched or proven otherwise, modified radical mastectomy remains the mainstay of present day therapy. For Stage II patients, similiar surgery and endocrine-chemotherapy regimens in combination or sequence offer the greatest promise of long-term survival. Although the correlation of estrogen receptors and the response rate to cytotoxic chemotherapy in metastatic breast cancer is as yet conflicting (1,5,17,19,), more recent data indicate that ER+ Stage IV breast cancer patients respond at least as well to chemotherapy. However, because of the relative lack of toxicity in endocrine therapy, an initial trial of hormone therapy should be attempted first in these patients.

In all clinical trials, therapeutic strategy should encompass hormone receptors, as well as the number of involved nodes. We support Meakin (26) who suggests that in future studies investigators must examine the role of adjuvant hormonal therapy, both as a complement to and as an alternative to adjuvant chemotherapy in patients with positive steroid receptors and involved nodes. We urge all surgeons, whenever possible, to enter breast cancer patients in well designed clinical trials. Only by such cooperative endeavors can progress be made against this devastating affliction.

SUMMARY

1. Hormone receptor assays in breast cancer tissue are useful markers for prediction of hormone sensitivity of the tumor.
2. In Stage I and II breast cancer, receptor assay has prognostic value for disease-free and total survival.
3. Endocrine adjuvant treatment for estrogen receptor positive breast cancers in both pre and postmenopausal women has been shown to be effective.
4. Whenever possible, both estrogen and progesterone receptors should be measured on tumor tissue from all breast cancer patients.

LEGENDS

Fig. 1. Sources of estrogen in premenopausal women. "Reproduced from Stoll (1969) by permission of the Publisher."

Fig. 2. Adrenal source of estrogen in postmenopausal women.

Fig. 3. Recurrence-free survival distributions of ER+ (≥ 3 fmols.) and ER- (<3 fmols.) Stage I breast cancer patients.

Fig. 4. Recurrence-free survival distributions of Stage I breast cancer patients with primary tumors greater and less than 2 cm in diameter.

Fig. 5. Disease-free recurrence distributions of Stage I premenopausal patients with breast cancer by estrogen receptor measurement.

Fig. 6. Disease-free recurrence distributions of Stage I postmenopausal patients with breast cancer by receptor measurement.

Fig. 7. Survival distriubtions of ER+ and ER- Stage I breast cancer patients.

Fig. 8. Schema of Beta protocol for Stage II ER+ premenopausal breast cancer patients.

Fig. 9. Schema of Beta protocol for Stage II ER+ postmenopausal breast cancer patients.

Fig. 10. Schema of Beta protocol for all Stage II ER- breast cancer patients-similar therapy for both pre and postmenopausal patients.

Fig. 11. Recurrence distributions of ER+ premenopausal Stage II breast cancer patients. OT vs. OT+5 drug.

Fig. 12. Comparison of recurrence distributions of ER+ premenopausal Stage II patients between Alpha and Beta Studies.

Fig. 13. Recurrence distributions of ER+ postmenopausal patients. T vs T+5- drug.

Fig. 14. Recurrence distributions for all ER+ Stage II breast cancer patients. T vs T+5-drug.

39-154 O - 84 - 16

Fig. 15. Recurrence distributions for all ER+ and ER- Stage II breast cancer patients.

Fig. 16. Disease-free survival curves compared with Estrogen Receptor and Progesterone Receptor status. From Clark et al. N. Eng. J. Med. 309: 1983 - by permission.

Fig. 17. Disease-free survival curves compared with Progesterone-Receptor levels From Clark et al N. Eng. J. Med. 309: 1983 - by permission.

Fig. 18. Disease-free survival curves compared with Estrogen-Receptor levels. From Clark et al N. Eng. J. Med. 309: 1983 - by permission.

TABLE I

Summary to March 1, 1984 of Beta protocol patients (See Text)

R-recurred D-died MI-died of myocardial infarction prior to recurrence

1. Allegra JC, Lippman ME: Estrogen receptor determination predicts response to tamoxifen therapy. Recent Results Cancer Res 71:16-19, 1980.

2. Beatson GT: On the treatment of unoperative cases of carcinoma of the mamma: Suggestions for a new method with illustrative cases. Lancet 2:104-107,1896.

3. Bryant AJS, Wain JA: Prophylactic oophorectomy in operable instances of carcinoma of the breast. Surg Gynecol Obstet 153:660-664, 1981.

4. Clark GM, McGuire WL, Hubay CA, et al: Progesterone receptors as a prognostic indicator for stage II breast cancer. N Engl J Med 309:1343-1347, 1983.

5. Cocconi G, DeLisi V, Boni C, et al: Chemotherapy verus combination of chemotherapy and endocrine therapy in advanced breast cancer. A prospective randomized study. Cancer 51:581-588, 1983.

6. Cole MP: Suppression of ovarian function in primary breast cancer. In: APM Forrest, PB Kunkler (eds): Prognostic Factors in Breast Cancer. E & S Livingston, Edinburgh, 139-145, 1968.

7. Cole MP: A clinical trial on an artificial menopause in carcinoma of the breast. INSERM: Hormones and Breast Cancer (Les Editions de l Institut National de la Sante et de la Recheiche Medicale 55:143-150, May 1975.

8. Cooper RG, Holland JF, Glidwell O: Adjuvant chemotherapy of breast cancer. Cancer 44:793-798, 1979.

9. Crowe JP, Hubay CA, Pearson OH, et al: Estrogen receptor status as a prognostic indicator for stage I breast cancer patients. Breast Cancer Res Treat 2:171-176, 1982.

10. Crowe JP, Gordon NH, Hubay CA, et al: The prognostic importance of estrogen receptor levels for stage I breast cancer patients. Current Surgery 41:No.1 24-26, 1984.

11. Hubay CA, Pearson OH, Marshall JS, et al: Adjuvant chemotherapy, antiestrogen therapy and immunotherapy for stage II breast cancer: 45-month follow-up of a prospective randomized clinical trial. Cancer (Suppl) 46:2805-2808, 1980.

12. Hubay CA, Pearson OH, Marshall JS, et al: Adjuvant chemotherapy, anti-estrogen therapy and immunotherapy for stage II breast cancer. In: HT Mouridsen, T Palshof (eds): Breast Cancer-Experimental and Clinical Aspects. Pergamon, Elmsford, N.Y, 189-195, 1980.

13. Hubay CA, Pearson OH, Marshall JS, et al: Adjuvant therapy of stage II breast cancer: 48-month follow-up of a prospective randomized clinical trial. Breast Cancer Res Treat 1:77-82, 1981.

14. Hubay CA, Pearson OH, Marshall JS, et al: Antiestrogen, cytotoxic chemotherapy, and Bacillus Calmette-Guerin vaccination in stage II breast cancer: a preliminary report. Surgery 87:494-501, 1980.

15. Hubay CA, Gordon NH, Crowe JP, et al: Antiestrogen-cytotoxic chemotherapy and Bacillus Calmette-Guerin vaccination in stage II breast cancer 72 month follow-up. Surgery (In Press).

16. Jensen EV, Block GE, Smith S, et al: Estrogen receptor and breast cancer response to adrenalectomy. In: TC Hall (ed): Prediction of Response in Cancer Therapy. Bethesda, National Cancer Institute: Monograph 34:55-70, 1971.

17. Kiang DT, Frenning DH, Goldman AI, et al: Estrogen receptors and responses to chemotherapy and hormonal therapy in advanced breast cancer. N Engl J Med 299:1330-1334, 1978.

18. Knight WA, Rivkin SE, Glucksberg H, et al: Adjuvant therapy of breast cancer: The Southwest Oncology Group Experience. Breast Cancer Res Treat 3 (Suppl 1):27-33, 1983.

19. Lippman ME, Allegra JC, Thompson EB, et al: The relation between estrogen receptors and response rate to cytotoxic chemotherapy in metastatic breast cancer. N Engl J Med 298:1223-1228, 1978.

20. McCarty KS, Hiatt KB, Budwet DA, et al: Clinical response to hormone therapy correlated with estrogen receptor analyses. Arch Path and Lab Med 108:24-26, 1984.

21. Manni A, Pearson OH: Antiestrogen-induced remissions in premenopausal women with stage IV breast cancer: Effects on ovarian function. Cancer Treat Rep 64:779-785, 1980.

22. Manni A, Arafah B, Pearson OH: Estrogen and progesterone receptors in the prediction of response of breast cancer to endocrine therapy. Cancer 46(Suppl):2838-2841, 1980.

23. Manni A: Hormone receptor and breast cancer. N Engl J Med 309:1383-1385, 1983.

24. Meakin JW, Allt WEC, Beale FA, et al: Ovarian irradiation and prednisone following surgery for carcinoma of the breast. In: SE Salmon, SE Jones (eds): Adjuvant Therapy of Cancer. North-Holland Pub Co., NY, 95-99, 1977.

25. Meakin JW, Allt WEC, Beale FA, et al: Ovarian irradiation and prednisone following surgery and radiotherapy for carcinoma of the breast. Can Med Assoc J 120:1221-1229, 1979.

26. Meakin JW, Allt WEC, Beale FA, et al: Ovarian irradiation and prednisone following surgery and radiotherapy for carcinoma of the breast. Breast Cancer Res Treat 3(Suppl 1):45-48, 1983.

27. Mouridsen HT, Palshof T, Rose C: Therapeutic effect of tamoxifen alone versus tamoxifen in combination with gestagen and oestrogen in advanced breast cancer. Recent Results Cancer Res 71:169-177, 1980.

28. Nissen-Meyer R: Suppression of ovarian function in primary breast cancer. In: APM Forrest, PB Kunkler (eds): Prognostic Factors in Breast Cancer. E and S Livingston, Edinburgh, 139-145, 1968.

29. Nissen-Meyer R: Ovarian suppression and its supplement by additive hormonal treatment. INSERM: Hormones and Breast Cancer 55:151-158, May 1975.

30. Oxley DW: Hormone receptors in breast cancer. Arch Path and Lab Med 108:20-23, 1984.

31. Pearson OH, Hubay CA, Marshall JS, et al: Adjuvant endocrine therapy, cytotoxic chemotherapy and immunotherapy in stage II breast cancer: five-year results. Breast Cancer Res Treat 3(Suppl 1): 61-68, 1983.

32. Pearson OH, Manni A, Arafah B: Antiestrogen treatment of breast cancer: an overview. Cancer Res 42:3424-3429, 1982.

33. Stoll BA: Clinical experience with tamoxifen in advanced breast cancer. Recent Results Cancer Res 71:207-211, 1980.

34. Stoll BA: Recent developments in the endocrine treatment of breast cancer - experimental and clinical aspects. Oxford, Pergamon, 79-80, 1979.

35. Ravdin RG, Lewison EF, Slack NH, et al: Results of a clinical trial concerning the worth of prophylactic oophorectomy for breast carcinoma. Surg Gynecol Obstet 131:1055-1064, 1970.

36. Weiss RB, Tormey DC, Holland H, et al: A randomized trial of post operative Five-vs-Three-Drug chemotherapy after mastectomy: A Cancer and Leukemia Group (CALGB) Study. Recent Results Cancer Res 80:170-176, 1982.

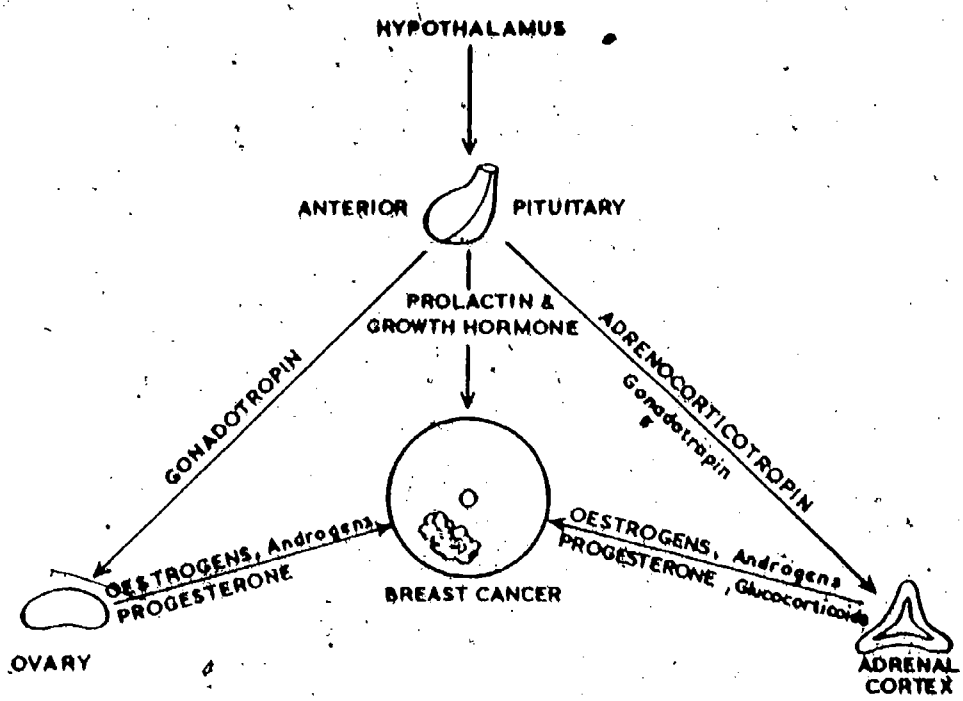

HYPOTHALAMUS
ANTERIOR
PITUITARY
PROLACTIN &
GROWTH HORMONE
GONADOTROPIN
ADRENOCORTICOTROPIN
Gonadotropin
OESTROGENS, Androgens
PROGESTERONE
OESTROGENS, Androgens
PROGESTERONE, Glucocorticoids
BREAST CANCER
OVARY
ADRENAL
CORTEX

FIG. 1

SOURCE OF POSTMENOPAUSAL ESTROGEN

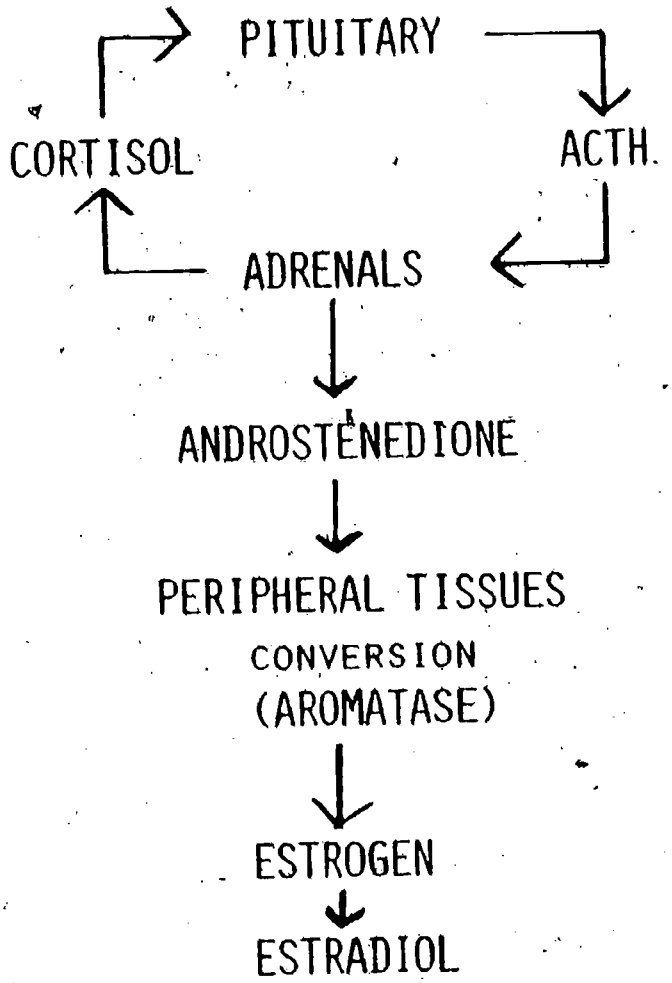


FIG. 2

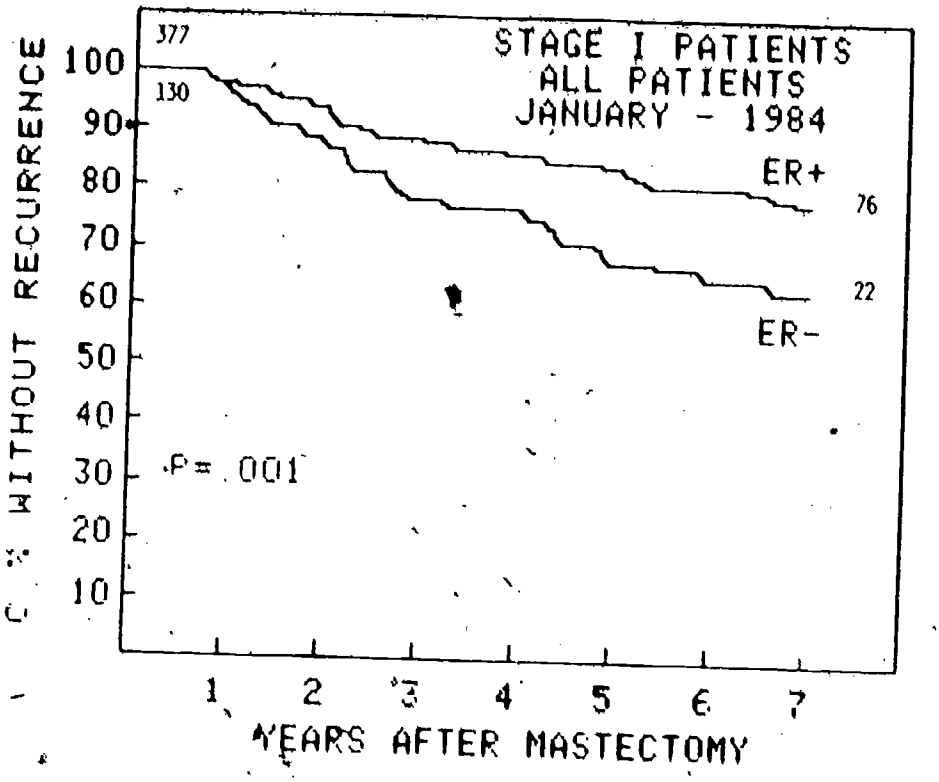

STAGE I PATIENTS
ALL PATIENTS
JANUARY - 1984
377
130
ER+
76
22
ER-
P= .001
% WITHOUT RECURRENCE
100
90
80
70
60
50
40
30
20
10
1
2
3
4
5
6
7
YEARS AFTER MASTECTOMY

FIG. 3

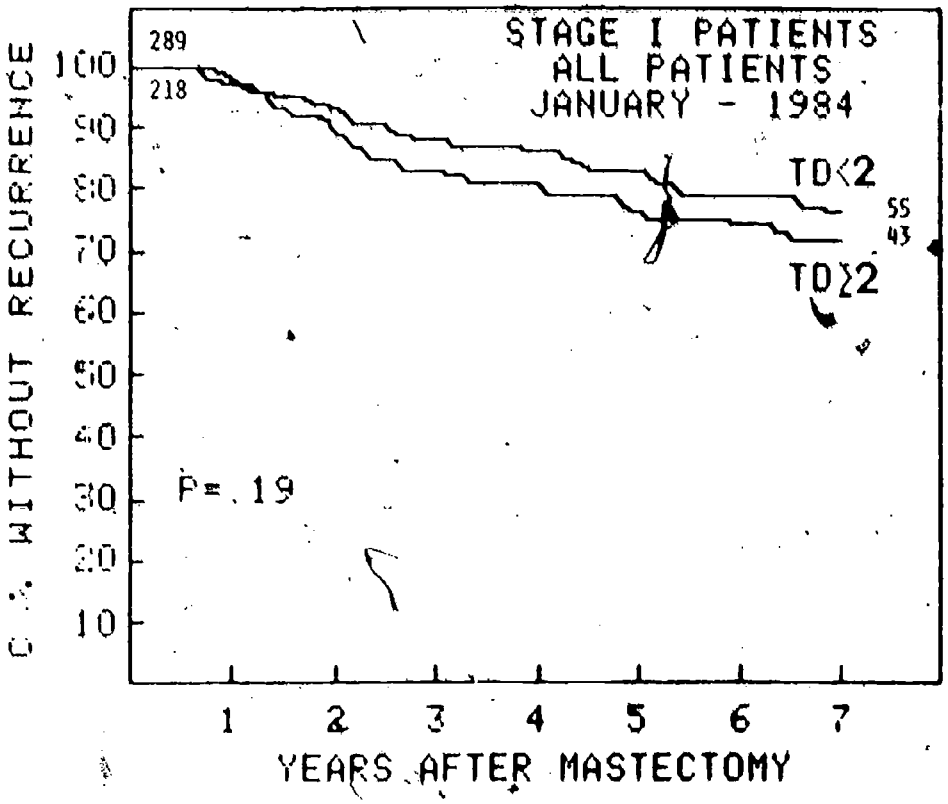

STAGE I PATIENTS
ALL PATIENTS
JANUARY - 1984
289
218
TD<2
55
43
TD≥2
P=.19
% WITHOUT RECURRENCE
100
90
80
70
60
50
40
30
20
10
1
2
3
4
5
6
7
YEARS AFTER MASTECTOMY

FIG. 4

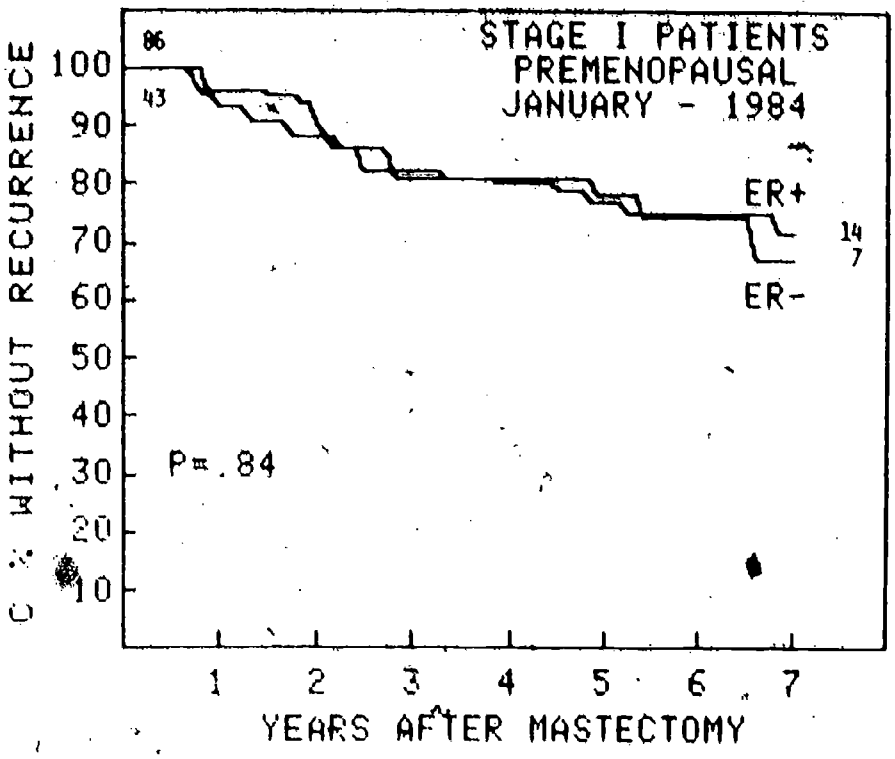

STAGE I PATIENTS
PREMENOPAUSAL
JANUARY - 1984
86
43
ER+
14
7
ER-
P=.84
% WITHOUT RECURRENCE
100
90
80
70
60
50
40
30
20
10
1
2
3
4
5
6
7
YEARS AFTER MASTECTOMY

FIG. 5

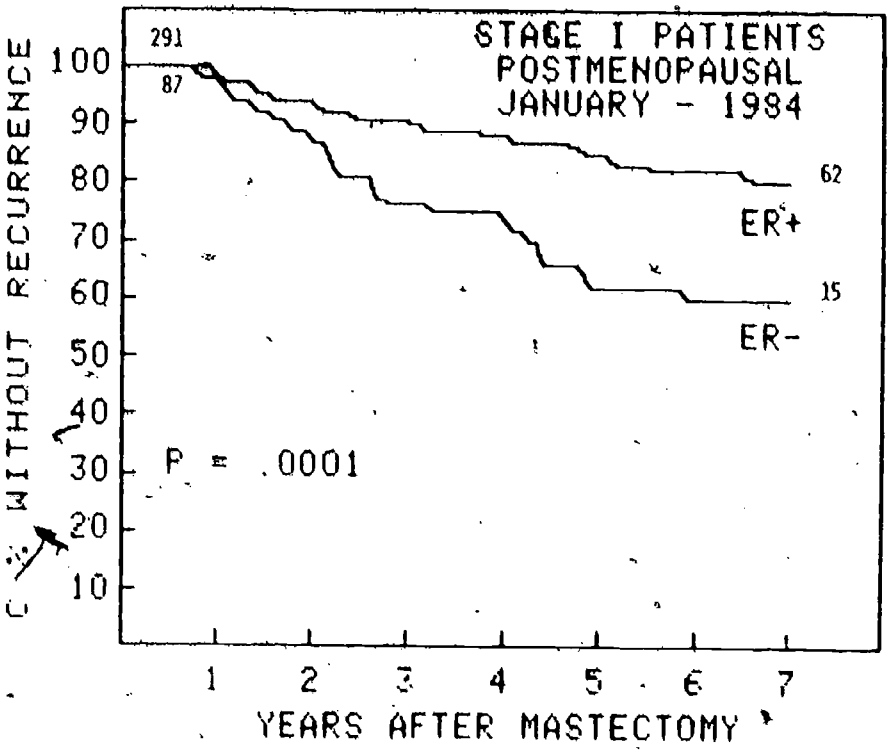

STAGE I PATIENTS
POSTMENOPAUSAL
JANUARY - 1984
291
87
62
ER+
15
ER-
P = .0001
% WITHOUT RECURRENCE
100
90
80
70
60
50
40
30
20
10
1
2
3
4
5
6
7
YEARS AFTER MASTECTOMY

FIG. 6

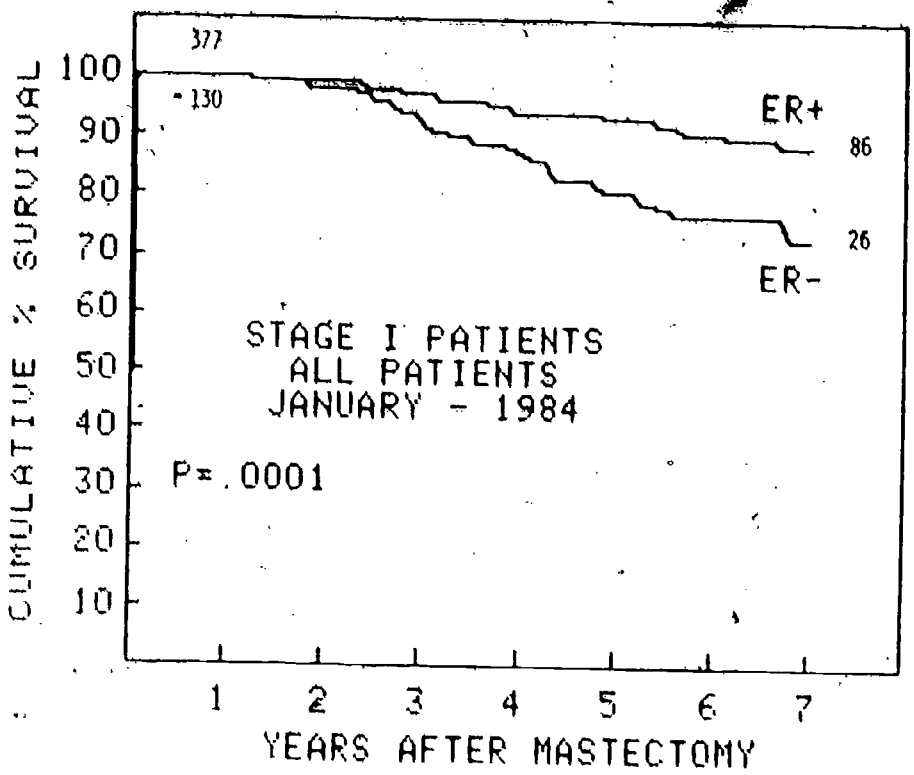

377
130
ER+
86
26
ER-
STAGE I PATIENTS
ALL PATIENTS
JANUARY - 1984
P=.0001
CUMULATIVE % SURVIVAL
100
90
80
70
60
50
40
30
20
10
1
2
3
4
5
6
7
YEARS AFTER MASTECTOMY

FIG. 7

ER+ PREMENOPAUSAL
ELIGIBLE STAGE II - III BREAST CANCER

1. MODIFIED RADICAL
2. OOPHORECTOMY

RANDOMIZED

TAMOXIFEN
3 YRS.

(1YR.) 5-DRUG + TAMOXIFEN
2 YRS. TAMOXIFEN

FIG. 8 -

ER+ POSTMENOPAUSAL
ELIGIBLE STAGE II - III BREAST CANCER
1. MODIFIED RADICAL

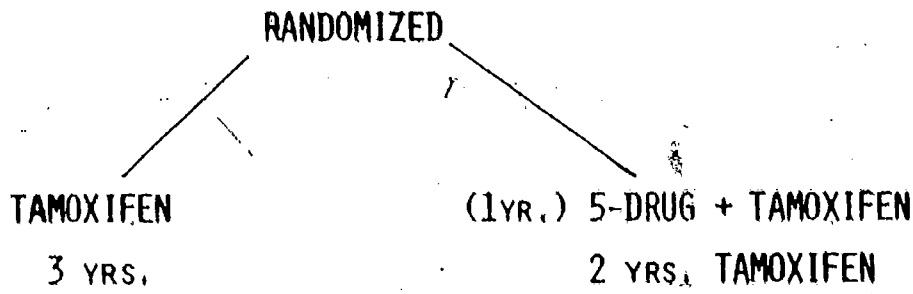


FIG. 9

ALL ER- PATIENTS

ELIGIBLE STAGE II - III BREAST CANCER

MODIFIED RADICAL

PREMENOPAUSAL

POSTMENOPAUSAL

(1YR.) 5-DRUG

FIG. 10

STAGE II - BETA

MARCH 1, 1984

			R	D
ER+ PRE	O + T	19	1	0
ER+ PRE	O + T + 5-D	15	3	1
ER+ POST	T	39	9	4 (1-MI)
ER+ POST	T + 5-D	36	2	3 (1-MI)
ER-	5-DRUG	24	6	5
		133	21	

TABLE I

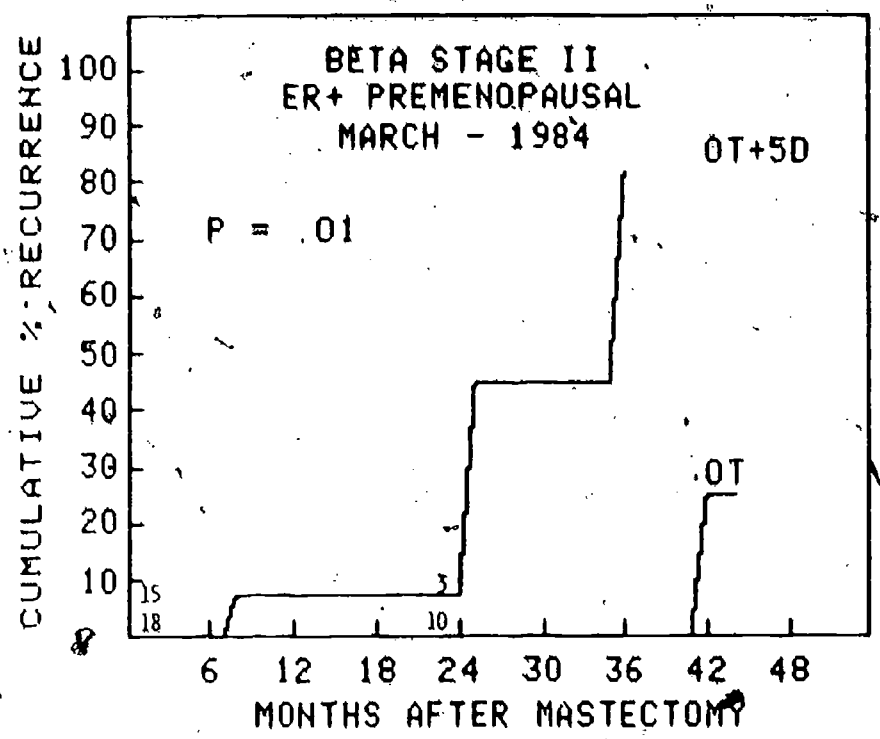

BETA STAGE II
ER+ PREMENOPAUSAL
MARCH - 1984
OT+5D
P = .01
OT
CUMULATIVE % RECURRENCE
100
90
80
70
60
50
40
30
20
10
0
15
18
3
10
6
12
18
24
30
36
42
48
MONTHS AFTER MASTECTOMY

FIG. 11

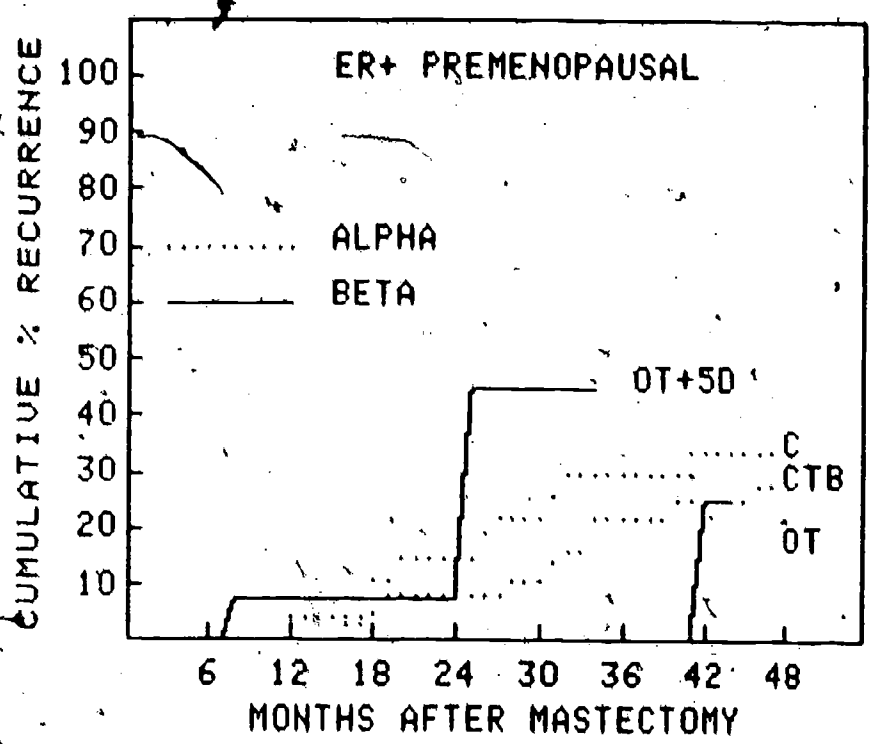

ER+ PREMENOPAUSAL
CUMULATIVE % RECURRENCE
100
90
80
70
60
50
40
30
20
10
ALPHA
BETA
OT+5D
C
CTB
OT
6
12
18
24
30
36
42
48
MONTHS AFTER MASTECTOMY

FIG. 12

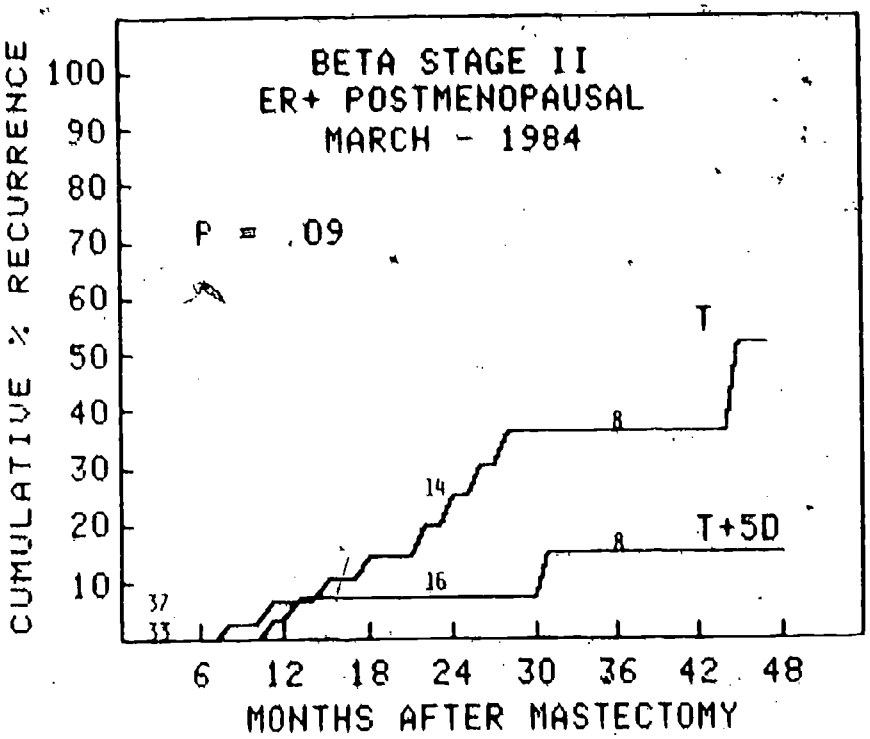

BETA STAGE II
ER+ POSTMENOPAUSAL
MARCH - 1984
P = .09
T
T+5D
8
14
16
8
37
33
CUMULATIVE % RECURRENCE
100
90
80
70
60
50
40
30
20
10
6
12
18
24
30
36
42
48
MONTHS AFTER MASTECTOMY

FIG. 13

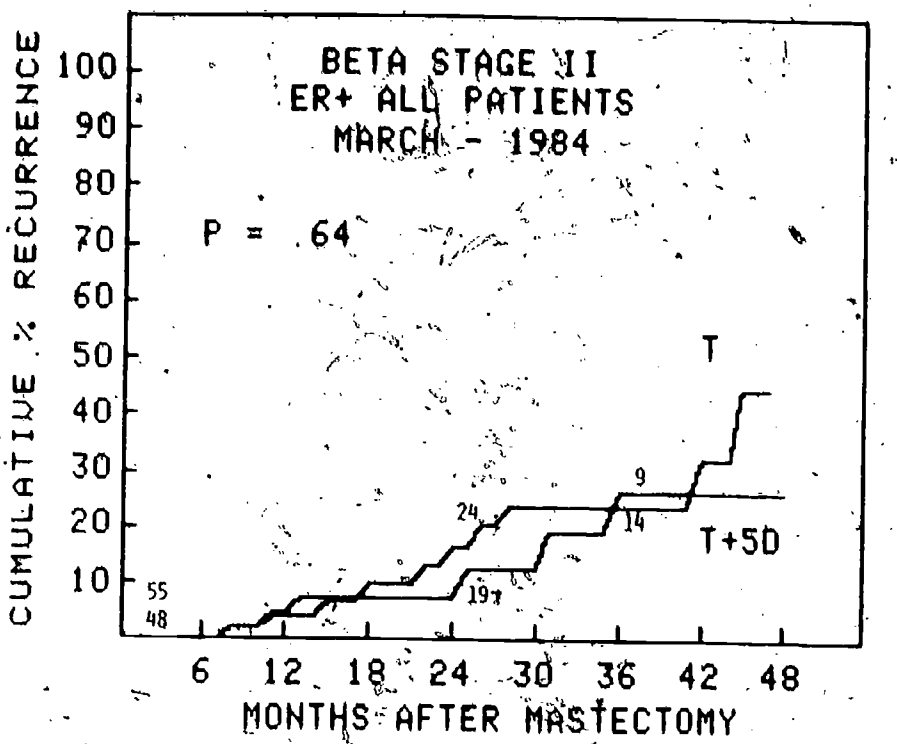

BETA STAGE II
ER+ ALL PATIENTS
MARCH - 1984
P = .64
CUMULATIVE % RECURRENCE
100
90
80
70
60
50
40
30
20
10
T
T+5D
9
14
24
19
55
48
6
12
18
24
30
36
42
48
MONTHS AFTER MASTECTOMY

FIG. 14

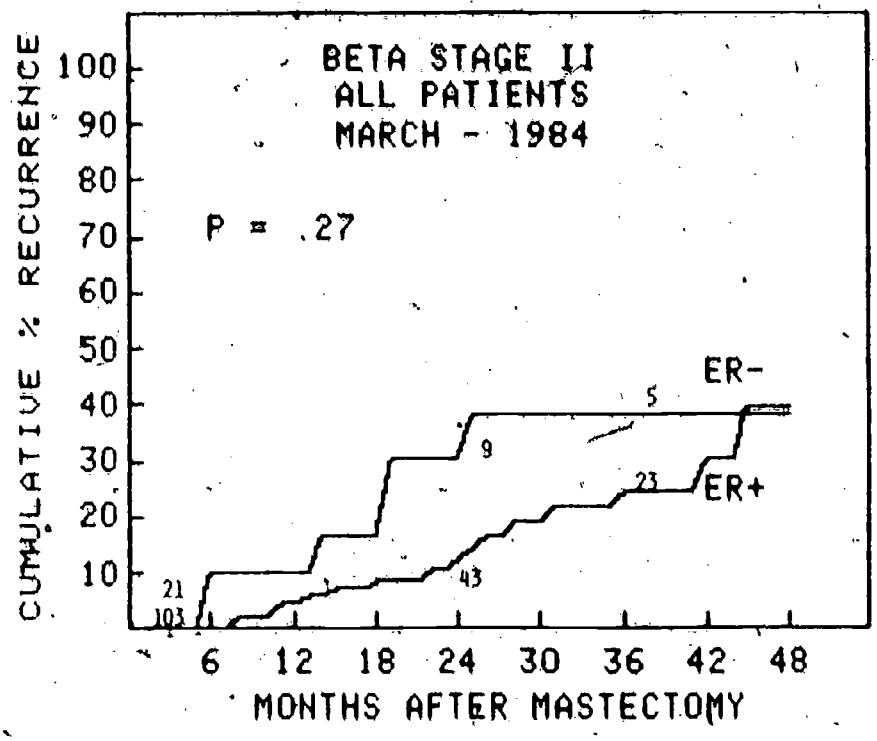
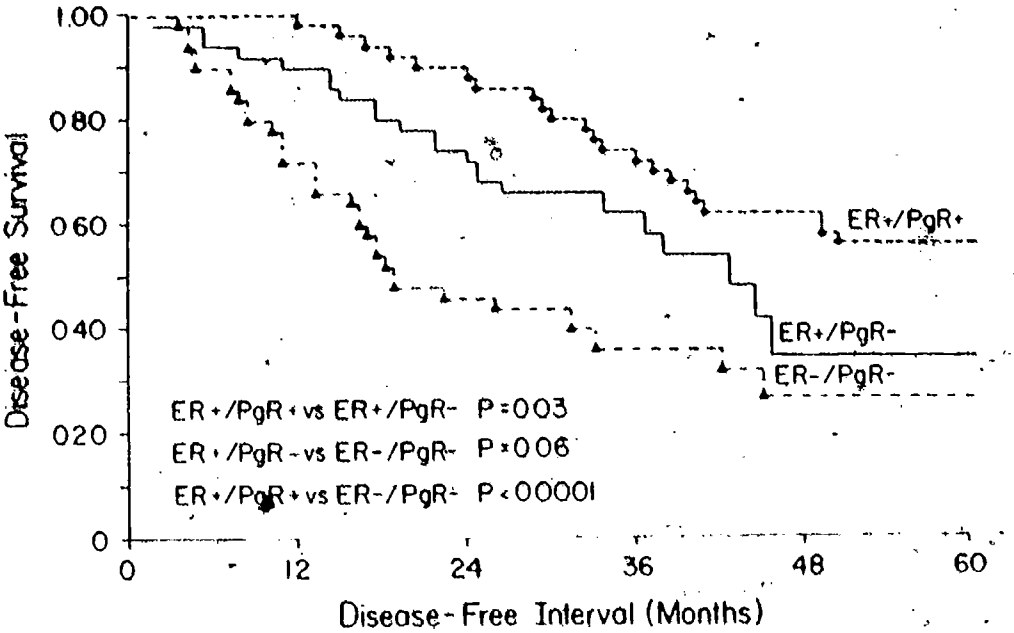
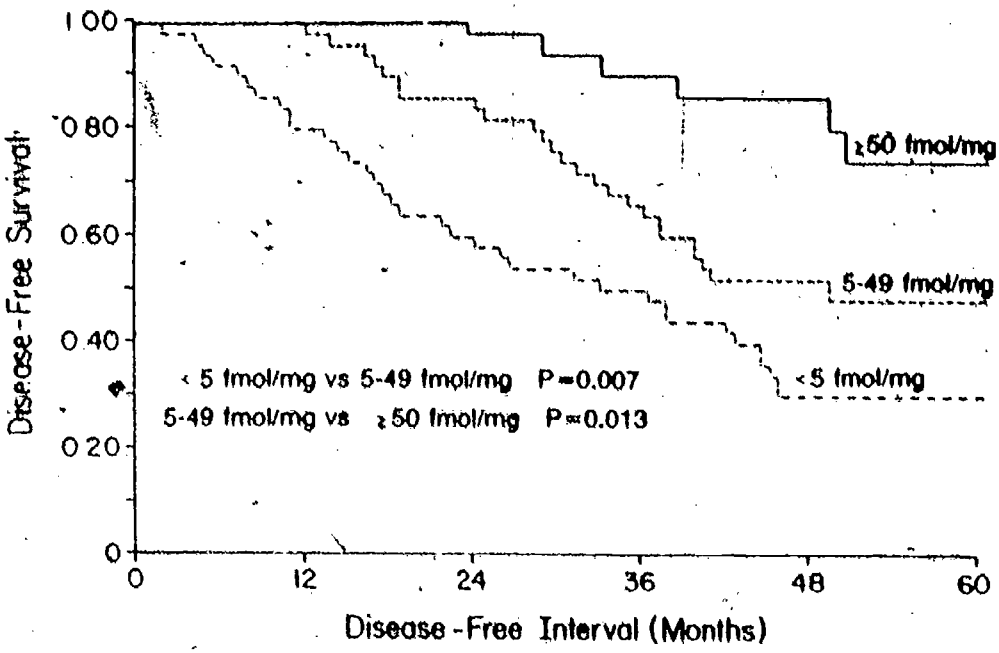

BETA STAGE II
ALL PATIENTS
MARCH - 1984
P = .27
CUMULATIVE % RECURRENCE
100
90
80
70
60
50
40
30
20
10
ER-
ER+
5
9
23
43
21
103
6
12
18
24
30
36
42
48
MONTHS AFTER MASTECTOMY

FIG. 15



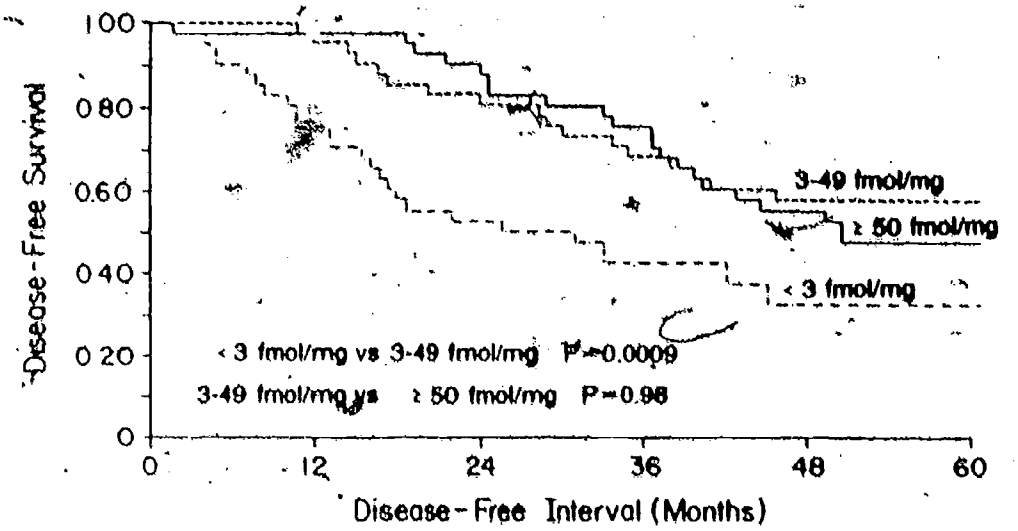
Disease-Free Survival Curves Compared with Estrogen-Receptor and Progesterone-Receptor Status.

FIG. 16



Disease-Free Survival Curves Compared with Progesterone-Receptor Levels.

FIG. 17



Disease-Free Survival Curves Compared with Estrogen-Receptor Levels.

FIG. 18.

APPENDIX 3

THE LIVINGSTON-WHEELER MEDICAL CLINIC
ALLERGY AND IMMUNOLOGY
3232 DUKE STREET
SAN DIEGO CALIFORNIA 92110
TELEPHONE (619) 224 9815

June 26, 1984

To: Subcommittee on Health and Aging - Report on Breast Cancer

Since this is basically a report on breast cancer, I will not spend a great deal of time on the general cancer infection in man.

Cancer is now known to be an infectious disease, a concept now universally accepted. The infectious agents most recently characterized are called "viruses." However, in newer concepts of microbiology, it is also known that "viruses" can be DNA, RNA or both sequences derived from bacterial fragments. Since breast cancer, then, is a known infection to be as yet a fully identified infectious agent, then the concept of breast cancer, as well as all cancers, must be reevaluated. When the specific infectious sequences are identified, then their source must be evaluated.

Whether the infectious fragments evolve as a result of super-infection from external human and animal sources, or whether they emerge from resting endogenous precursors due to carcinogenic exposure, requires specific evaluation. There is some evidence that the external carcinogens cause emergence of the endogenous cellular agents which act together to produce neoplastic transformation.

Surgical removal of tumors can often be very useful, providing they are surgically accessible and not destructive of vital organs. Removal of tumors can provide a debulking effect which makes the neoplastic tissue more accessible to the action of antibodies. However, to state that a cure is affected by "getting it all," is nonsensical since the cancer disease is much more than a local tumor; it is a generalized systemic cancer condition consisting of a specific infection with marked lowering of immunity. It is well to build up the resistance of the individual patient before surgery. Resistance can be enhanced by dietary factors such as the use of the retinoids and carotinoids. I am the first to have discovered that abscisic acid, a retinoic acid related to the carotinoids, has a beneficial effect on restricting the spread of cancer. Also, the effect of chorionogonadotropic hormone on all tumors is now being explored. I am, in addition, the first person to demonstrate that the microbe, Progenitor Cryptocidos, produces a form of chorionogonadotropin. This hormone is essential to the evolvement of the neoplastic state.

This subject is too lengthy to go into detail at this time; however, it might be mentioned that the hormones in breast cancer are vitally involved. For instance, prolactin, the hormone essential for the stimulation of milk production is present in all lactating mammals, both in animals and man. It is wise for the woman who has breast cancer to avoid the use of milk products since there is a heavy production of prolactin in the lactating cow. Also, there are other growth hormones involved in the

Subcommittee on Health & Aging
June 26, 1984

rapid growth of young calves that are inappropriate for use in the patient with neoplasia.

The subject of breast cancer is very extensive. There are a number of kinds of breast cancer. The simplest are small nodules developing after fibrocystic mastitis, a benign disease of the breast. This disease is readily controlled by appropriate measures and removes the prodromal cancer state. The simpler cancers, which are small and may be removed by a lumpectomy, can be controlled by appropriate immunotherapy or surgery, plus limited radiation. However, if dietary and immunotherapy measures are not combined with simple removal in the absence of positive nodes, then the future control of the local tumor is not assured. Some forms of breast cancer are extremely virulent from the beginning. One notable type is inflammatory cancer, even if this is recognized early in the course of the disease, it is not controlled by surgery, so that even finding a lump and removing it is not applicable to some forms of cancer.

In general, there are preventive cancer measures consisting of Bacillus Calmette Guerin (BCG) administration in solid tumors as well as leukemia. Dr. Sol Roy Rosenthal, Professor of Preventive Medicine at the University of Illinois reports use of BCG on 85,000 children prior to 1972 which resulted in markedly reduced cancer incidence in those up to 12 years of age. (JAMA, 1972, V222, p. 543) In the Bulletin of the Pasteur Institute (1983, V83, p. 55-83), 74% of the individuals BCG immunized remained cancer free for twenty years.

Dr. Anthony Strelkauskas, Associate Professor of Pediatrics at the Medical University of South Carolina, has demonstrated that a number of patients treated at the Livingston-Wheeler Clinic showed unusually high antibodies, not only in breast cancer, but in many other cancers. In your possession is the letter to this effect from Dr. Strelkauskas. A combination of BCG and a vaccine made from Progenitor Cryptocides could be universally adopted for prevention. Not only can monoclonal antibodies be produced, but their presence is a guide to the progress of treated patients. Dr. Strelkauskas is willing to come before the Committee on this subject.

Since the use of chemotherapy is practically ineffectual in the treatment of breast cancer in regard to longevity, the use of monoclonal antibodies after the disease has erupted as well as extensive use of immunotherapy is strongly indicated.

These statements are preliminary, very brief and not sufficiently comprehensive to give more than a superficial view of the subject. The entire problem of not only breast cancer, but of all cancers is a matter to be discussed in great detail as soon as feasible. These statements are submitted in the hope that sufficient interest will be aroused to continue further investigation in depth. Our work in these areas mentioned is based on solid research of many years duration.

Respectfully submitted,

Virginia C. Livingston Wheeler, M.D.

VCLW:dg
enclosures

IOWA VALLEY COMMUNITY COLLEGE DISTRICT

ADMINISTRATIVE OFFICES 3700 South Center St Box 838 Marshalltown Iowa 50158 Phone (515) 752-4643

June 14, 1984

JUN 18 1984

Dr. Virginia Livingston-Wheeler
Livingston-Wheeler Foundation for Research
of Cancer and Allied Diseases
3232 Duke Street
San Diego, CA 92110

Dear Dr. Virginia:

I am a community college president and lost my wife to breast cancer three months ago. Recently my family physician, Dr. Axel (Ted) Lund, told me of your work and I have now read Conquest of Cancer, a few of your earlier papers on this subject, and even happened to see you on Iowa television. Remarkable, since I thought I'd researched the waterfront looking for such cancer material while my wife was alive, yet never once came across your name. This brings us to the subject of my letter.

Among the most exasperating problems in dealing with cancer is the dearth of knowledge available to the lay person about viable alternative cures. The typical information through the cancer institutes, with few exceptions, is worthless and very often out-dated, geared to newspaper-level intellect. Media coverage of "wonder cures" are quackery in themselves and a show of irresponsible reporting. Worse, the lulling effects on Americans unaffected by this disease is monumental. Whether or not your particular research would have helped my wife, or whether she would have even considered attending your clinic, is beside the point. To me, the infuriating issue is that - after spending considerable time these past three years in searching, writing, and phoning various sources - I did not even hear of your work.

In some way, I'd like to be able to help change that for other lay people. Those similarly afflicted should at least have the knowledge of what your staff is doing. With your permission, I would like to visit with you at your clinic. I need to be in California for a conference, and could probably be in San Diego for a few hours, during the first week of July. I would like to explore the possibility of having you discuss your methods, findings, and whatever, with an audience of Iowans through an interstate telenetwork system available at community college sites in our state. I'm sure there are many who would take note of your work, and you wouldn't even have to leave San Diego. I will phone your offices probably on July 2nd to confirm an hour which might be convenient for you.

Wishing you every success, I am,

Sincerely,

John [redacted]hoda, Ed.
Superintendent/President

JJP/ld

United States Patent [19]

Livingston

[11] 3,958,025

[45] May 18, 1976

[54] ABSCISIC ACID TABLETS AND PROCESS

[76] Inventor: Virginia W.C. Livingston, 8492 Prestwick Drive, La Jolla, Calif. 92037

[22] Filed: July 5, 1974

[21] Appl. No. 485,846

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 295,220, Oct. 5, 1972, which is a continuation-in-part of Ser. No. 82,806, Oct. 21, 1970, abandoned, which is a continuation-in-part of Ser. No. 831,982 June 10, 1969, Pat. No. 3,768,249, which is a continuation-in-part of Ser. No. 490,679, Sept. 27, 1965

[52] U.S. Cl. 424/317

[51] Int. Cl. A61K 31/19

[58] Field of Search 424/317

[56] References Cited

OTHER PUBLICATIONS

The Merck Index, 8th Ed., Merck & Co., Inc., 1968, p. 1711.

Primary Examiner—Stanley J. Friedman

Attorney, Agent, or Firm—Christen & Sabol

[57] ABSTRACT

Tablets of abscisic acid and a carrier are used to treat a vitamin deficiency of abscisic acid in man, animal and the avian species.

14 Claims, No Drawings

UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 3,958,025 Dated May 18, 1976

Inventor(s) Virginia W.C Livingston

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

In the patent heading, item [63], Related U.S. Application Data, line 4, cancel "831,982" and insert therefor --831,985--.

In the patent heading item [63], Related U.S. Application Data, line 5, cancel "Pat. No. 3,768,249" and insert therefor --abandoned--.

In the patent heading, item [63], Related U.S. Application Data, line 7, between "1965" and the period, insert --, abandoned--.

Signed and Sealed this

Eleventh Day of October 1977

[SEAL]

Attest:

RUTH C. MASON
Attesting Officer

LUTRELLE F. PARKER
Acting Commissioner of Patents and Trademarks

1

ABSCISIC ACID TABLETS AND PROCESS

BACKGROUND OF THE INVENTION

This is a continuation in part application of copending application Ser. No. 295,720, filed Oct. 6, 1972, which is a continuation in-part of copending application Ser. No. 82,806, filed on Oct. 21, 1970, now abandoned, which is a continuation-in-part application of, and was copending with application Ser. No. 831,982, filed on June 10, 1969, now U.S. Pat. 3,768,249, which is a continuation in-part application of, and was copending with, application Ser. No. 490,629, filed on Sept. 27, 1965.

DESCRIPTION OF THE INVENTION

This invention involves a method of treating a vitamin deficiency of abscisic acid in man, animal and the avian species. The process includes administering to the man, animal or avian species a composition comprising abscisic acid and a carrier. The abscisic acid is administered to the man, animal or avian species in an amount from 10mcg. to about 20 mg. per kg. of body weight per day. This invention also involves the composition containing the abscisic acid and carrier.

Evidence for the etiological relationship of Progenitor cryptocides to neoplastic disease has been documented over a period of years. Its cultural properties, staining characteristics, and morphology have been fully described. Its filterable bodies have been measured by electron microscope and found similar in size to some viruses. The pathology produced in experimental animals has been reported. It has also been demonstrated in fresh blood samples examined by darkfield and phase microscopy. More recently, immunological studies in guinea pigs have shown cross-reactivity with *M. tuberculosis*. In addition, the production by *P. cryptocides in vitro* of a parathormone or analogue of human chorionic gonadotropin is described. Its identification by bioimmunological and radioimmunoassay methods has been established.

2

SKIN REACTIONS OF GUINEA PIGS IMMUNIZED WITH CRYPTOCIDES, BCG, AND MYCOPLASMA HOMINIS TO MYCOBACTERIAL PURIFIED PROTEIN DERIVATIVES (PPD)

This was an experiment to determine how guinea pigs immunized against cryptocides, BCG, Tumor Homogenates, and Mycoplasma hominis would react to intradermal skin tests with purified protein derivatives derived from six different mycobacterial strains. Forty-two white female guinea pigs weighing from 300 – 350 grams each were distributed in groups of six into seven cages. Each group received from 0.15 to 0.2 ml of immunizing antigen every three days. Six doses were given intraperitoneally to all but those animals receiving live BCG, which was administered only once.

PROCEDURE

The immunizing antigens were: I. Cryptocides in formalinized pooled blood cultures; II Cryptocides in the German vaccine, from various mixed tumor homogenates; III. phenolized Mycoplasma hominis, cultured from a freshly isolated genital strain; and IV. BCG attenuated bovine tubercle bacilli, lyophilized organisms. Control animals received no immunization.

After a rest period of one week following immunization, the guinea pigs were shaved on both sides, and intradermal skin tests were performed with 25 units (0.0005 mgm per 0.1 ml.) of PPDs derived from six different strains of mycobacteria, a suspension in 0.5% phenol of 2% phenol killed cryptocides organisms. The animals were examined for any skin reactions developing within 24 to 48 hours. The results are presented in the included table.

The similar skin reactions shown by guinea pigs immunized by cryptocides strains, Mycoplasma hominis, and BCG tubercle bacilli to the various mycobacterial PPDs and cryptocides, demonstrate antigen sharing and interrelationship between cryptocides, the Mycobacteria, and Mycoplasma hominis.

The BCG immunized guinea pigs gave slightly stronger reactions to the mycobacteria PPD than to the cryptocides suspension. However, this was a suspension of whole bacteria and products rather than a purified protein.

SKIN TEST REACTION* OF GUINEA PIGS AFTER I.P. IMMUNIZATION WITH CRYPTOCIDES, BCG, AND M. HOMINIS

Immunizing Antigens	PPD Seibert	PPD Bailey	PPD Strohschein	PPD Fontana	PPD Kawasaki	PPD Avian	Killed Cryptocides
I Cryptocides blood cultures	++	++	+	+	±	++	++
II Cryptocides urine cultures	++	+	+	+	+	+	++
III *Suspension of formalinized pooled human tumor homogenates	++	+	++	+	+	+	++
IV Mycoplasma hominis	±	±	+	±	±	±	+
V BCG bovine Tubercle bacilli	++	++	++	+	+	++	+
VI Controls no	–	–	–	–	–	–	±

*++ = redness and swelling
+ = redness, no swelling
± = slight redness
– = no redness, no swelling

*Vaccine produced by Albrecht & Co., Undenheim, Germany

dermatitis. It is planned to produce PPD from cryptococcus to be used as a standard testing material.

PROGENITOR CRYPTOCIDES AS A PRODUCER OF AN ANAHORMONE OR PARAHORMONE: CHORIONIC GONADOTROPIN IN VITRO

The toxic fractions obtained from tumor isolates of P. cryptocides have been previously described.[1] Cultures of P. cryptocides grown in the dark at room temperature yield a dark, red-brown material when extracted with a mixture of n-butanol, glacial acetic acid and water. Reddish plates, oily residue and white crystals were observed. Similar material was obtained. A typical yield from 150 ml. urine sample gave approximately 20 mg. of needlelike crystals, 5 mg. of the oil, and 10 mg. of the red plates. The combined amounts appeared to represent activity of about 0.5 mg/day secreted in urine. The material at this time was not identified. However, the entire toxic endproducts were shown to increase the incidence of tumors in mice two and a half-times in the twenty week pulmonary bioassay test. Suspension of the material was demonstrated to exhibit some antibiotic properties. The white crystalline material was not separated from the red plates and oily substances at that time.

Since the mouse experiments with the entire crystalline material demonstrated an increase in the incidence of tumors that there might be a specific growth factor in the cultures of P. cryptocides. This factor is believed to be chorionic gonadotropin. With this thought in mind, cultures of P. cryptocides were grown and extracted for chorionic gonadotropin. Under certain specific cultural conditions which are readily reproducible, it was found that CGH is produced in relatively large amounts by P. cryptocides in vitro.

PREPARATION AND DEMONSTRATION OF CHORIONIC GONADOTROPIN PRODUCED BY PROGENITOR CRYPTOCIDES IN VITRO

BACTERIAL METHODOLOGY

I. Culture media

The culture media has been fluid thioglycollate medium without indicator. The dry mixed medium is purchased in 1 lb. bottles and prepared as directed so that each liter furnishes the following.

	Grams per liter
Tryptone	17.0
Phytone	3.0
Dextrose	5.0
Sodium chloride	2.5
Sodium thioglycollate	0.5
Agar	0.7
L-cystine	0.75
Sodium sulfite	0.1

30 grams of the dehydrated material is suspended in a liter of distilled water and heated on a Corning hot plate agitated by a magnetic stirring bar. Heating is continued for about 2 minutes after boiling. The medium is then sterilized in an autoclave at 120°C., 15 lbs. pressure for 15 minutes.

II. Organism

The organism used for innoculation of the sterile broth is a single colony from blood agar plates (phenylethyl alcohol). The organism is from patient urine isolates or blood cultures which exhibit acid-fastness. Incubation is carried out on an incubator at 37°C. The flasks are gently rocked. The incubation time has varied from 9 to 21 days. In all cases the growth produced good turbidity in 3 to 4 days. The time of maximum CGH production has not been established. However, little CGH is detected before the ninth day of incubation.

III. Isolation of the CGH

The entire culture media, organisms and broth are acidified to pH 4.5 – 5.0 by the addition of glacial acetic acid (75–100 ml. per 10 liters). Next 4 volumes or 40 liters of C.P. acetone are added to the 10 liter mixture producing a white precipitate.

The mixture is allowed to sit overnight at room temperature and the precipitate is recovered either by filtration or centrifugation. The final precipitate is washed with 10 ml. of dry acetone and then allowed to air dry after decanting the acetone supernatant.

This air dried fraction is always colored (tan or reddish brown). 10 mg. of this crude material dissolved in 10 ml. of distilled water is then used in the Pregnosticon test system. In the actual test only 0.1 ml. is used. The reaction is almost always a plus 4 reading.

Further purification of the CGH-like material can be done by resuspending the sample in distilled water. The CGH-like material is water soluble whereas the proteins and associated lipids are water insoluble. Centrifugation and/or filtration at this stage will remove the oily substances and reddish plates to yield grey-white crystals. The CGH can be reprecipitated from the water phase with 4 volumes of acetone. The oily substance and reddish plates are yet to be further characterized.

The following score system was used:

No reaction	less than 250 I.U./liter	0	0
	250–2,500 I.U./liter		1
	2,500–25,000 I.U./liter		2
	25,000–325,000 I.U./liter		3
	Over 325,000 I.U./liter		4

The results are presented in the following table.

CHORIONIC GONADOTROPIN DETERMINATIONS IN CONTROL ORGANISMS.

NAME	VISUAL SCORE	CULTURE ORGANISM URINE	BIOASSAY
Staphylococcus Aureus	neg		neg
Pseudomonas Aeruginosa	neg		neg
Salmonella Typhosa	neg		neg
Bacillus Subtilis	neg		neg
Proteus Mirabilis	neg		neg

THE EFFECT OF CHORIONIC GONADOTROPIN FROM VARIOUS SOURCES ON MATURE FEMALE MICE

I. 5 mice Saline Control 0.25 ml/mouse per day for 10 days given I.P.

II. 5 mice 1000 I.u. of commercial human chorionic gonadotropin, 0.25 ml. I.P.

III. 5 mice 1000 I.u. of human chorionic gonadotropin, isolated from urine specimens, a composite of positives by Organon Immuno-assay 0.25 ml/I.P.

IV 5 mice 1000 i.u. of gonadotropin isolated from cryptococcus cultures administered in 0.25 ml daily.

The mice were sacrificed after weighing

The following were determined.

Adrenal weight.

Ovary weight

Uterine weight

Any differences in body weight.

MOUSE EXPERIMENT WITH CHORIONIC GONADOTROPIN

	Mouse No	2/1/73 Wt g	2/11/73 Wt g	Diff Mouse	Adrenal Wt mg	Ovary Wt mg	Uterine Wt mg
SALINE CONTROL	1	28	30.0		5.1	39	125
	2	26	29.0		5.0	50	130
	3	26	31.0		5.6	56	130
	4	27	33.0		4.9	31	135
	5	25	34.0		5.3	28	140
	Total	132	157		25.9	164	650
	Av	26.4	32.5	6.1	5.18	32.8	130
HCG COMMERCIAL PREPARATION	6	29	21.0		4.1	42	102
	7	25	16.0		5.2	46	130
	8	26	20.0		3.5	43	[illegible]
	9	27	24.0		3.7	44	112
	10	28	25.0		4.2	49	121
	Total	135	106		18.7	224	868
	Av.	27.0	21.2	-5.8	3.74	44.8	173.6
URINE CGH	11	26	27.0		5.1	54	130
	12	26	24.0		3.8	36	140
	13	29	23.0		4.9	37	145
	14	31	24.0		4.3	29	142
	15	30	25.0		4.1	31	141
	Total	142	123		22.1	167	698
	Av	28.4	24.6	-3.8	4.4	33.2	139.6
ORGANISM GONADOTROPIN	16	31	24.0		4.7	35	145
	17	26	26.0		4.3	30	130
	18	27	26.0		4.2	36	136
	19	26	23.0		4.1	33	138
	20	27	23.0		3.8	34	140
	Total	137	122		21.1	168	709
	Av	27.4	24.4	-3.0	4.2	33.6	141.8

Body weight loss was similar.

Only the commercial CGH affected the uterine weight.

Following the mouse experiments, biological testing with rats was performed as follows: Female Sprague-Dawley rats were injected intraperitoneal with the respectively materials listed below. The total volume of each injection was 0.25 ml per day for the 4 week period. Each group was composed of 10 rats.

Group	Material injected
I	Saline control
II	Pooled urine chorionic gonadotropin isolated

Group	Material injected
	when diluted

It is believed that the HCG produced by the cryptocides by neutralized by abscisic acid, an antigrowth hormone of plants. The tests demonstrate that this inhibition did occur in vitro using as little as 100 micrograms of abscisic acid per liter of culture media inocu-

lated with cryptocides. The HCG was negative in the treated sample at the end of nine days whereas the untreated control cultures were rated 4 plus.

The abscisic acid was obtained from Calbiochem of La Jolla, Lot No. 300032 which was synthesized in pure crystalline form by Hoffman-LaRoche Inc.

The animals were weighed on day 1 and then at weekly invervals. At 28 days the animals were again weighed and sacrificed. The ovarian weights were determined at this time. Results:

Summary of weight gain and ovarian weights of rats treated with various chorionic gonadotropins and/or like materials.

	Initial Wt	Final Wt	Wt Gain g	Ovarian wt, mg.
I Saline	96.2	179.0	100.8	26.5
II Urine CGH material	85.8	126.9	41.1	23.9
III Bacterial CGH material	87.5	124.9	37.4	28.2
IV Control CGH	87.2	143.5	56.3	40.7

from patients having a 3 or 4 plus Pregnosticon Test. The final material had a 4 plus activity and was suspended in saline

III Bacterial chorionic gonadotropin-like material isolated from a composite of cryptococcus organism (12 day culture in thioglycollate medium). The final saline soluble material resulting from acetone precipitation had an activity of 2 plus using the Pregnosticon test

IV Control chorionic gonadotropin, manufactured by Rice Biologicals, Los Angeles, California, Lot No. 73F 166 which contained 1000 USP units/ac

URINE PREPARATION METHOD

Determination of chorionic gonadotropin was performed on acetone precipitate of 100 ml. aliquot of a 24 hour urine from the patient. The remainder of the test was carried out using the immuno-diagnostic pregnancy test (Pregnosticon®) manufactured by Organon. The range of international units was determined by dilution of precipitate.

The bacterial or cryptocides isolate represented 1 billion organisms/cc in 25 ml To each 25 ml suspension without further treatment, was added 100 ml. acetone The precipitate was discarded. CGH determinations were carried out on the water soluble portion.

It is apparent from the above Tables that CGH produced in the urine of patients with neoplastic disease as well as the CGH like material produced by the cryptocides organism has a growth inhibiting or wasting effect on mice and rats The same CGH like material had little or no effect on increasing the ovary weights of the animals

RADIOIMMUNOASSAY TECHNIQUE FOR ISOLATION OF CGH DERIVED FROM PROGENITOR CRYPTOCIDES

Lyophylized bacterial preparation was reconstituted with 5 ml distilled water. 100 µl of this preparation together with a tracer of ^{125}I Human Chorionic Gonadotropin (100,000 counts/min) was applied to the surface of a 1 × 15 cm column of polyacrylamide molecular exclusion gel "Biogel P-4". The column was eluted with 0 02 M phosphate buffer, pH 7.35, and collected in 0 5 ml. fractions. The bulk of the radioactivity was recovered in tubes 6, 7, 8, 9 and 10 (3-5 ml). These fractions were combined, and this was assayed for CGH by radioimmunoassay, sensitive to 0 25 MIU ? Two other later fractions (No 24 and No. 63) were assayed at the same time The combined early fraction was found to contain a large amount of HCG, with a potency exceeding 10 IU per 10µl or reconstituted preparation The other two fractions contained no HCG. Thus, the fact that the material emerged from the gel column at precisely the same fraction as authentic ^{125}I HGC, coupled with its specific immuno-reactivity toward anti HCG in the radioimmunoassay, strongly suggests its close identity with chorionic gonadotropin, with respect to both its molecular weight and size, and its immunological properties

The following hormones were checked and found absent in the bacterial extract Cortisol, testosterone, thyroid stimulating hormone (TSH), growth hormone (GH) and follicle stimulating hormone (FSH)

The antiserum made against the whole extract of cryptocides and that made against the purified fraction (HCG) from cryptocides were both positive when checked with HCG, that is, they both found HCG in an antibody antigen reaction

It has been demonstrated that a filter passing pleomorphic microbe, P cryptocides appears to be etiologically involved in the production of neoplastic disease in man and animals It has been classified as belonging to the Actinomycetales and is intermittently acid-fast Its pathology for experimental animals has been demonstrated It is a blood parasite in both man and animal It can be cultured readily on appropriate media from tumors and body fluids Recently it has been shown that it cross reacts with a number of mycobacteria such as BCG, and Mycoplasma hominis when tested in the guinea pig Toxic fractions from the cultures are known to increase the incidence of tumors in controlled mouse experiments These fractions contain not only toxic antibiotic materials not characterized as yet but also crystalline material which appears to be CGH as such or as an analog or anthormone as demonstrated in experimental animal studies and by radioimmunoassay. The production of CGH by P cryptocides in vitro may explain the occurrence of the paraendocrine syndromes found in neoplasia.

SIGNIFICANCE OF THE EXPERIMENTAL EVIDENCE THAT CHORIONIC GONADOTROPIN IS PRODUCED BY PROGENITOR CRYPTOCIDES IN VITRO

Recent evidence that human chorionic gonadotropin antiserum appears to slow down experimental tumors in mice has been presented by Y.N. Sinha, Scripps Institution in La Jolla. Breaking the chain of host dominance by the bacterial CGH may prove to have therapeutic value? The bacterial counterfeit polypeptide CGH appears to subvert from normal physiological pathways many complicated endocrine processes of the human host by action upon the pluripotential immature cell causing it to revert to its atavistic or primitive reproductive state since CGH is concerned with rapid growth of embryonic or immature tissues before differentiation and maturation occur. CGH and subsequently bacterial CGH acts as a dominant hormone having the power to direct and alter many endocrine processes either by primary synthesis or related polypeptides or by secondary stimulation of steroidgenesis. Early in the neoplastic disease, destruction of tumor cells may benefit the host as might the reduction in numbers of the invading microbial parasite but late in the disease, endocrine and metabolic processes may be irreversibly damaged by the parasitic CGH so that removal of the tumor cells and destruction of the microbes may not restore normal endocrine balance since damage to the vital hormonal, immunological, enzymatic and metabolic processes may be irreversible and irreparable. Hope for the future may lie in universal vaccination or, barring that, early recognition of impending hormonal and immunological imbalance.

The Production of HCG In Vitro by Progenitor Cryptocides Its Neutralization by Abscissic Acid In Vitro and In Vivo.

Abscisic acid (dormin), a plant hormone occurring naturally in certain parts of plants of many varieties, is known to produce a state of dormancy in roots and seeds as well as to cause leaf abscission and ripening of fruits, has been synthesized by Hoffman La Roche This action of A.A. in inducing dormancy of plants, roots and seeds opposes the growth promoting action of the gibberlins and auxins.

The microbe, Progenitor Cryptocides a member of the Order Actinomycetales previously described at length, produces in vitro a hormone immunologically identical to the human growth hormone, chorionic gonadotropin However, in vivo the microbic hormone does not produce genital hyperplasia in mice and rats as does the human hormone.

Since fungi and some related microbes produce hormones similar to those of plants, it was proposed by the applicant (VWCL) that the microbic chorionogonadotropin, a growth factor, might be opposed or neutralized by a growth retardant, A A Both the crude plant extract containing only 30% of the A.A., and the pure synthesized A A from Hoffman La Roche did prove to inhibit the production of microbic HCG in vitro Progenitor cryptocides was implanted into two one liter flasks of suitable media. Into one flask 10 micrograms of A A was added to the culture. The other flask received no A A At the end of nine days, there was no microbic chorionogonadotropin present by assay in the

flask containing the Cryptocides and A A The growth of the microbes was 3+ as judged by turbidity The control flask not inoculated with A A showed 4+ growth and the equivalent of 750,000,000 units of chorionogonadotropin as assayed.

Following the in vitro experiments, the in vivo study of an animal tumor model was undertaken for determination of survival rate of C57BL/6J mice with C1498 transplated tumor following treatment with abscisic acid.

The mice and the transplanted tumor stock were purchased from The Jackson Laboratory, Bar Harbor, Maine The mice were all males. The animals were housed in polypropylene cages and were fed Purina Laboratory Chow and water ad libitum.

The tumors were excised from the stock animals and transplanted to the animals used in this experiment. Treatment was started the day following the tumor transplantation The 1498 tumor is a myeloid leukemia. It is palpable in 3-5 days and is lethal to the host in 10-15 days.

Abscisic acid, lot No. 001022, furnished by Hoffmann-LaRoche Inc was suspended in saline and administered as a suspension Treatment was carried out for a total of 7 days. The following schedule was used:

Group	Treatment	Dose per Kilo body Wt	No. mice per Group
I	Saline 0.1 ml Intraperitoneally (I P.)		10
II	Abscisic acid, 10 mcg (0.1 ml.) I P.	10	10
III	Abscisic acid, 100 mcg (0.1 ml.) I P.	100	10
IV	Abscisic acid, 100 mcg (0.1 ml.) oral	100	10
V	Abscisic acid 1000 mcg (0.1 ml.) oral	1000	10

Results

At the end of 14 days The following survivors were noted.

Group and Treatment	No. Survivors
I Control Saline I P	3
II 1 mg/kg abscisic acid, I P	9
III 10 mg/kg abscisic acid, I P	10
IV 10 mg/kg abscisic acid, oral	6
V 100 mg/kg abscisic acid, oral	9

All of the remaining animals appeared to have palpable tumors

It was concluded that abscisic acid has a marked effect in the inhibition of the C1498 tumor system in the C57Bl/6J mouse The compound is effective by the intraperitoneal and oral route.

The presence of plant root growth inhibiting substances in human serum and urine has been demonstrated by sephadex G-10 fractionation. R F Scand Jr. Clinic Lab Invest., pp. 25-32, Jan 70 Thus, the serum of healthy persons can be demonstrated to have a higher inhibiting effect on plants than that of the sick or aftmath, that is, a greater amount of the inhibitory factor exists in the blood of the well person See Analogs of abscisic Acid and/or Dormancy Hormone Structure and Activity C R Academy of Science (D) Paris 270 1936-1939, 13 April 1970, Mousselon - Canet M., Mani, Durand, etc.

Radio immuno assay studies on the rabbit serve to further evidence that the presence of abscisic acid neutralizes the tumor growth factor and thereby, in effect, assists in the prevention of tumors in mice.

In vitro studies conducted in a 2 liter flask containing the cryptocides produced COH in contrast to an untreated bottle which exhibited brown microbes at a 4 plus level measurable at the end of 10 days in terms of 750,000,000 units of COH. In a further study, 10 mcg. of abscisic acid produced no COH and inhibited microbes growth to about 3 plus.

It was observed that abscisic acid apparently is nontoxic in the mouse even when administered I.P. in amounts of up to 10% by weight of the mouse Thus, with a 28 gram body weight mouse, I.P. administered at 2800 mg per week had no apparent adverse effects.

Abscisic acid and its analogs may be employed in pure form and preferably in a pharmaceutical carrier and may be administered orally or parenterally Also impure forms of abscisic acid and its analogs such as extracts of naturally occurring sources usually of the order of 30% purity also may be administered.

Abscisic acid and its analogs are described in The Merck Index, Eighth Edition, page 1711 Synthetic methods for the production of abscisic acid and its analogs are described in U.S. Pat. Nos. 3,576,880, 3,793,375 and 3,803,217.

Abscisic acid and its analogs also may be employed in the treatment of animals and the avian species in the form of feed additives or in humans as a dietary supplement. Thus, cattle feed and chicken feed may be fortified with amounts of abscisic acid up to the above mentioned dosage. It is believed that abscisic acid or its analogs may be an essential food element and component in man, animal and avian species, much akin to the well known essential vitamins as employed in dietary supplements in man and in feed additives in animals and avian species where deficiencies are known to exist Thus, if an abscisic acid deficiency exists, it can be treated as herein stated

REFERENCES

1. Wuerthele Gaspe V. (Livingston), and R. N. Alleo 1948 Microorganisms associated with neoplasms. N.Y. Microscopical Soc. Bull. 2: 2 - 31.

2. Wuerthele-Caspe, V. (Livingston), E. Alexander-Jackson, J. A. Anderson, J. Hilber, R. M. Allen, and L. W. Smith 1959 Cultural properties and pathogenicity of certain microorganisms obtained from various proliferative and neoplastic diseases. Amer. J. Med Sci. 230: 628-646.

3. Alexander-Jackson, E. 1954. A specific type of microorganism isolated from animal and human cancer, bacteriology of the organism Proc. VIth Int. Cong. Microbiol. Section XVII A. Rome, Italy, Sept. 1953. Growth 18: 37-51.

4 Alexander Jackson, E. 1966 Mycoplasmas (PPLO) isolated from Rous sarcoma virus. Growth 30: 199-228.

5 Diller, I. C. 1963. Growth and morphological variability of three similar strains of intermittently acid-fast organisms isolated from mouse and human malignant tissues. Growth 26: 181-208.

6 Diller, I. C. and W. Diller. 1965. Intracellular acid-fast organisms isolated from malignant tissues. Trans. Amer. Micr. Soc. 84: 138-148.

7 Villequez, E. J. 1955. Le Parasitisme Latent des Cellules du Sang chez l'Homme, en Particulier dans le Sang des Cancereux. Maloine, Paris, France.

8 Manklewicz, E. 1965. Antigenic components shared by bacteriophages, and phage hosts mycobacteria, Corynebacteria, and Hela Cells. Growth 29: 125-139.

9 Mazet, G. 1962. Presence d'elements alcoolo-acido resistants dans les moelles leucemiques et les moelles non leucemiques. La Semaine des Hopitaux (Medicine dans le Monde) 38 e Annee. 1-2: 35.

10 Seibert, F. B., F. K. Farrelly, and C. C. Shepard. 1967. DMSO and other combatants against bacteria isolated from leukemia. Ann. N.Y. Acad. Sci. 141: 175-201.

11 Seibert, F. B., F. M. Feldman, R. L. Davis, and I. S. Richmond. 1970. Morphological, biological, and immunological studies on isolates from tumors and leukemic blood. Ann. N.Y. Acad. Sci. 174: art. 2, 690-728.

12 Inoue, S., M. Singer, and J. Hutchinson. 1965. Causative agent of a spontaneously originating visceral tumor of the newt Triturus. Nature 205: 408-409.

13 Pease, P. E. 1967. Tolerated infection with the sub bacterial phase of Listeria. Nature 215: 936-938.

14 Livingston, V. Wuerthele-Caspe, and E. Alexander Jackson. 1970. A specific type of organism cultivated from malignancy: bacteriology and proposed classification. Ann. N.Y. Acad. Sci. 174, art. 2: 630-654.

15 Alexander Jackson, E. 1970. Ultraviolet spectrographic microscope studies of Rous sarcoma virus cultured in cell free medium. Ann. N.Y. Acad. Sci. 174, art. 2, 765-781.

16 Livingston, V. Wuerthele-Caspe, and E. Alexander Jackson. 1970. A specific type of organism cultivated from malignancy: bacteriology and proposed classification. Ann. N.Y. Acad. Sci. 174, art. 2, 636-654.

17. Alexander Jackson, E. 1954. Atypical forms of pathogenic mycobacteria. Int. Record Med. Gen. Practice Clinics 167: 7: 389-397.

18 Alexander-Jackson, E. 1945. A hitherto undemonstrated zoopleal form of Mycobacterium tuberculosis. Ann. N.Y. Acad. Sci. 46: 127-152.

19 Wuerthele Caspe, V. (Livingston), E. Alexander Jackson, and L. W. Smith. 1953. Some aspects of the microbiology of cancer. J. Amer. Med. Wmn. Ass. 8: 7-12.

20 Wuerthele-Caspe, V. (Livingston), and E. Alexander Jackson. 1965. An experimental biologic approach to the treatment of neoplastic disease. J. Amer. Med. Wom. Ass. 20: 858-866.

21 Wuerthele Caspe, V. (Livingston). 1953. Microbiology of Cancer. A study of a specific microorganism isolated from animal and human cancers: Its identification in tissue. The immunologic aspects with diagnostic and therapeutic Pros. 14th Int. Cong. Microbial. Section XVII A. Rome, Italy.

22 Leyton, A. S. and H. Leyton. 1916. Observations on the aetiology of sarcoma in the rat. Lancet i: 513.

23 Crotlon, W. M. 1936. The true nature of viruses. Staples Press Ltd. London, England.

24. Nuzum, J.W. 1925. Experimental production of metastasizing carcinoma in breast of dog, and primary epithelioma in man by repeated inoculation of Micrococcus isolated from human breast cancer. Surg. Gyn. Obstet. 11: 343-352.

25. Fanth, C. J. 1958. Etiohalogenese del Cancro. Amadeo Nicola and c. Milan, Italy.

26 Clark, G. A. 1953. Successful culturing of Glover's cancer organism and development of metastasizing tumors in animals produced by cultures from human malignancy. Proc. Cong. of Microbial. Rome, Italy.

27 Diller, I. C. 1962. Growth and morphological variability of three similar strains of intermittently acid-fast organisms isolated from mouse and human malignancy tissues. Growth 26: 181-208.

28 Inoue S., M. Singer, and J. Hutchinson. 1965. Causative agent of a spontaneously originating visceral tumor of the newt Triturus. Nature 205: 408-409.

29 Seibert, F. B., F. K. Farrelly and C. C. Shepherd. 1967. DMSO and other combatants against bacteria isolated from leukemia. Ann. N.Y. Acad. Sci. 141: 175-201.

30 Gerlach, F. 1948. Krebs und Obligater Pilzparasitismus. Urban und Schwartzenberg. Vienna, Austria.

31 Scott, M. J. 1926. Clinical experiences with carcinoma antitoxin. J. Cancer 9: 1-6.

32 Glover, T. J. 1930. The bacteriology of cancer. Canada Lancet Pract. 74: 92-111.

33 Glover, T. J., M. J. Scott, J. London, and M. McCormack. 1926. Study of Rous chicken sarcoma No. 1. Canada Lancet Pract. 46: 49.

34 Villequez, E. J. 1955. Le Parasitisme Latent des Cellules du Sang chez l'Homme, en particulier dans le sang de cancereux. Maloine, Paris, France.

35 Mazet, G. 1962. Présence d'elements alcoolo-acido resistants dans les moelles leucemiques et les moelles non leucemiques. La Semaine des Hopitaux (Medicine dans le Monde) 38 e Annee. 1-2:35.

36 Manklewicz, E. 1965. Antigenic components shared by bacteriophages, and phage hosts, mycobacteria, corynebacteria, and Hela cells. Growth 29: 125-139.

37. Diller, I. C. and W. Diller. 1965. Intracellular acid fast organisms isolated from malignant tissues. Trans. Amer. Micr. Soc. 84: 138-148.

38 MacPherson, I. Reversion in hamster cells transformed by Rous sarcoma virus. science 148: 1731, 1965.

39 Livingston, A. M., V. Wuerthele-Caspe Livingston, and E. Alexander-Jackson, and G. H. Walter. 1970. Toxic Fractions obtained from tumor isolates and related clinical implications. Ann. N.Y. Acad. Sci. 174 art. 2. 675-689.

40 Beard, J. The Enzyme Treatment of Cancer. 1911. Chatto and Windus, London, England.

41. Waldenstrom, J. G. 1970. Maladies of derepression, monoclonal derepressinn of protein forming templates. Schweiz. med. Wschr. 100. 2197-2206.

42 Gurdon, J. B. 1968. Transplanted nuclei and cell differentiation. Sci. Amer. 219. 24-35.

43 Alfsen-Norris Forrest, M. 1973 Syndromes hormonaux ectopiques Sem. Hop. Paris, 49, nn. 4 245-256.

44 Studer, H., J. J. Staub and F. Wyss. 1971. Schweiz. med. Wschr. 101, 446-447, Nr. 13.

45 Dilman, V. M. V.N. Golubev, N. V. Krylova. 1973 Dissociation of hormonal and antigenic activity of luteinizing hormone excreted in endometrial carcinoma patients (endogenous neohormones) Am. J. Obstet. Gynecol. 115, no. 7 966-971.

46 Livingston, Wuerthele-Caspe, V., A. M. Livingston. 1972. Demonstration of Progenitor Cytoxicides in the blood of patients with Collagen and neoplastic diseases. Transactions of N.Y. Acad. Sci. Series II, Vol 34, No 5 433-453

47 Canlow, M. J. R. and J. E. Johnson. 1967. J. Appl. Pol. Sci. II, 1851.

48 Midgley, A. R. Jr. 1966. Endocrinology. Vol. 79, 10

What is claimed is:

1. The method of treating a vitamin deficiency of abscisic acid in man, animal or the avian species, which comprises administering to said man, animal or avian species a composition comprising abscisic acid and a pharmaceutical carrier or food supplement or feed additive, said abscisic acid being administered to said man, animal or avian species in an amount from 10 mcg. to about 20 mg. per kg of body weight per day.

2. The method as described in claim 1 wherein the administration to said man, animal or avian species, is oral or parenteral.

3. The method of claim 1 wherein said composition is in the form of a tablet

4. The method of claim 1 wherein said pharmaceutical carrier is starch and flavoring

5. The method of claim 1 wherein said pharmaceutical carrier is a saline solution.

6. The process as described in claim 1 wherein said composition comprises a feed additive and abscisic acid.

7. The process as described in claim 1 wherein said composition comprises a pharmaceutical carrier and abscisic acid.

8. The process as described in claim 1 wherein said composition comprises a dietary supplement and abscisic acid.

9. The process as described in claim 1 wherein said abscisic acid is administered to said man, animal or avian species in an amount of about 10 mg per kg. of body weight per day.

10. The process as described in claim 1 wherein said abscisic acid is administered to said man, animal or avian species in an amount of about 10 mg per kg. of body weight per day.

11. A composition in tablet form for the treatment of a vitamin deficiency of abscisic acid in man, animal or the avian species which comprises abscisic acid, in an amount ranging from about 10 mcg. to 20 mg. per kg. of body weight per day, in admixture with a carrier.

12. The composition of claim 11 wherein said carrier is starch and flavoring.

13. The composition of claim 11 wherein said carrier is a feed additive base.

14. The composition of claim 11 wherein said carrier is a food supplement.

Description

METHOD FOR PREPARING A PURIFIED EXTRACTION RESIDUE FRACTION AND ITS USE IN STIMULATING THE IMMUNE RESPONSE

Technical Field

This invention relates to a method of preparing a water-soluble, purified extraction residue fraction (antigen) of a microorganism, the purified residue fraction itself, and its use in stimulating the immunological response in warm-blooded animals against a variety of tumors.

Related Application

This application is a continuation-in-part application of pending Serial No. 128,919, filed March 10, 1980, which is a continuation of Serial No. 957,206, filed November 3, 1978, now abandoned.

Background Art

The purified extraction residue fraction (antigen) of microorganisms described in detail hereafter has been found to be useful in the treatment of avian leukosis as well as in the treatment of warm-blooded animals, including man, by stimulation of their immune response against a variety of tumors. The microorganism from which the purified extraction residue fraction is obtained is a pleomorphic, refractile and filterable form of bacteria which has been repeatedly isolated from both human and animal malignant tissue and blood of tumor-bearing hosts. These bacteria have been described by many investigators, but not many agree on their taxonomy because of their pleomorphism. Using standard culture and fermentation techniques, they resemble common saphophytes. Their various growth phases have been described as viruses, depetheroids, micrococci, bacilli, and fungi. See V. W-C. Livingston and E. Alexander-Jackson, "A Specific Type of Organism Cultivated from Malignancy: Bacteriology and Proposed Classification," Ann. N. Y. Acad. Sci., 174:636-654 (1970); G. J. Domingue and J. U. Schlegel, "Novel Bacterial Structures in Human Blood: Cultural Isolation," Infection & Immunity, 15:621-627 (1977); and V. W-C. Livingston and A. M. Livingston, "Some

Cultural, Immunological and Biochemical Properties of Progenitor Cryptocides," Trans. N. Y. Acad. Sci., 36:569-582 (1974).

In 1970, Virginia Livingston-Wheeler and Eleanor Alexander-Jackson proposed a new taxon for this organism within the order Actinomycetale. They named the organism "Progenitor cryptocides." Progenitor cryptocides has been repeatedly isolated from human and animal malignant tumors and has many interesting features, such as pleomorphism, intermittent acid-fastness, a unique ability to pass through bacterial filters, and the ability to produce chorionic gonadotropin. See V. W-C. Livingston and E. Alexander-Jackson, "A Specific Type of Organism Cultivated from Malignancy: Bacteriology and Proposed Classification," Ann. N. Y. Acad. Sci., 174:636-654 (1970); and V. W-C. Livingston and A. M. Livingston, "Some Cultural, Immunological and Biochemical Properties of Progenitor Cryptocides," Trans. N. Y. Acad. Sci., 36:569-582 (1974).

The avian leukosis complex comprises the neoplastic diseases of the hematopoietic system of the domestic chicken, together with several other neoplastic and non-neoplastic conditions which are related either etiologically or pathologically. The following diseases are included in the complex leukosis: lymphoid leukosis, erythroid leukosis, and myeloid leukosis. Diseases etiologically related to leukosis include sarcoma, neophroblastoma, endothelioma and osteopetrosis. Marek's disease includes the neural form, visceral form and ocular form. See The Merck Veterinary Manual, 3rd edition, Merck & Co., Inc., New Jersey, pp. 1081-1091 (1976). Marek's disease, for example, is seen in birds three weeks of age onward to adults. The commonest is two to four months. Young chicks are more susceptible than older birds. Genetic factors strongly influence the response of birds to agents of the leukosis complex. See A. E. Churchill and P. M. Briggs, "Agent of Marek's Disease in Culture," Nature, London 215:28-530 (1967); and J. J. Solomon, R. L. Witter, K. Nazerian and B. B. Burmester, "Studies on the Etiology of Marek's Disease: Ch. I. Propagation of the Agent in Cell Culture," Proc. Soc. Exp. Biol. Med., 127:173-177 (1968). Avian leukosis is presumably caused by a group B herpes virus. See J. J. Solomon, R. L. Witter, K. Nazerian and B. B. Burmester, "Studies on the

Etiology of Marek's Disease: Ch. II. Finding of Herpes Virus in Cell Culture," Proc. Soc. Exp. Biol. Med., 127:177-182 (1968). A live but attenuated form of turkey herpes virus vaccine has been effective until recently in preventing the incidence of Marek's disease tumors; however, its effectiveness has markely declined. The mechanism of protection is not clear. Birds vaccinated develop a viremia with the vaccine. See Kermani-ARAB, V. T. Moll, D. R. Cho, W. D. Davis and Y-S. Lu, "Effect of Cyclophosphamide on the Response of Chickens to a Virulent Strain of Marek's Disease Virus," Infection & Immunity, 12:1058-1064 (1975). A group of investigators have just recently reported protection of chickens against Rous sarcoma virus with the use of methanol extracts of BCG challenged with Rous sarcoma. They also reported that chickens with palpable tumors, and then treated, developed necrosis of the tumor. See Y. Markson, F. Doljansky and D. W. Weiss, "Effects of Prophylactic Treatment with the Methanol Extraction Residue Fraction of Tubercle Bacilli (MER) on the Development of Rous Sarcomas of Chickens Following Challenge with the Rous Sarcoma Virus," Immunological Parameters of Host-Tumor Relationships, Vol. 5, D. W. Weiss (Ed.), Academic Press, New York, pp. 51-59 (1978).

Treatment of warm-blooded animals by subcutaneous injection of the purified extraction residue fraction is based on stimulation of the immune response of the host to the injected substance. Immunotherapy is a therapeutic approach to the treatment of cancer which is based on the concept that there are distinctive antigens in or on most tumor cells that distinguish them from normal host cells. Most tumor immunologists favor the view that potentially malignant cells constantly arise in the body; but because of their foreign nature, they are normally eliminated by the body's immune system. On occasion, however, tumor cells escape this immune surveillance and continue to reproduce, resulting in cancer. The reasons for the failure of this normally efficient immune mechanism are not completely understood. The body's immune system is depressed in certain genetic immunodeficiency diseases, in various bacterial, fungal or viral infections, and in patients undergoing immunosuppressive radiation therapy.

Experimental studies in animals have demonstrated the antitumor potential of a number of immunostimulants,

including live organisms of bacillus Calmette-Guerin (BCG), heat-killed cells of Corynebacterium parvum, polynucleotides and the anthelmintic drug, levamisole.

Stimulation of host resistance may be detected in animal models that can, in fact, detect both immunostimulators and anti-cancer agents. This is accomplished by infecting warm-blooded animals, such as mice, either with a virus which produces the disease and a disease-related immunodepression or with a transplantable mammary tumor. Effective agents for their therapeutic value are recognized by their ability to restore or enhance the antibody response in the experimental animal. Another means of recognizing stimulation of the immune response is to measure increased antibody responses or increased protective effects produced by the co-administration of vaccines and "immunoadjuvants." Further discussions of the function of immune response, methods of stimulation, and testing may be found in the following references: "Stimulation of Humoral and Cellular Antibody Formation in Mice by Poly I:C," W. Turner, et al., Proc. Soc. Exp. Biol. & Med., 133, 334-338 (1970), and "Humoral and Cellular Immune Responses in Susceptible and Resistant Strains of Mice Infected with Friend Leukemia Virus," W. S. Czlowski, et al., Proc. Soc. Exp. Biol. & Med., 146, 619-624 (1974).

The methanol extraction residue fraction of tubercle bacilli has been shown to be an activator and modulator of immunological responsiveness and capable of evoking pronounced therapeutic effects against a variety of tumors in laboratory mammals and man. See D. W. Weiss, "Nonspecific Stimulation and Modulation of the Immune Response and of States of Resistance by the MER Fraction of Tubercle Bacilli," Nat'l. Cancer Inst. Monogr., 35:157 (1972); D. W. Weiss, et al., "Nonspecific Stimulation of Antimicrobial and Antitumor Resistance and of Immunological Responsiveness by the MER Fraction of Tubercle Bacilli," in: A. Zuckerman and D. W. Weiss (Eds.), Dynamic Aspects of Host-Parasite Relationships, Vol. 1, Academic Press, New York, p. 163 (1973).

Disclosure of the Invention

This invention is concerned with a method of stimulating the immune response in warm-blooded animals by administering to the animals an effective immunostimulating

amount of a purified extraction residue fraction from a microorganism isolated from the blood or urine of a warm-blooded host of a malignant tumor of a host, the microorganism having the capacity to synthesize the polypeptide hormone known as "chorionic gonadotropin" in its total form or in its alpha and beta subunits. In particular, this invention is concerned with a method of stimulating the immune response in the avian species, such as domestic chickens, to avian leukosis by administering to the chickens an effective immunostimulating amount of a purified extraction residue fraction of the microorganism Progenitor cryptocides. The invention is also concerned with a method of preparing the purified extraction residue fraction from the microorganism and the residue fraction per se.

It is thus a principal object of this invention to provide a method for stimulating the immune response in warm-blooded animals by administering to the animal an effective immunostimulating amount of a water-soluble, purified extraction residue fraction of the microorganism Progenitor cryptocides.

It is a further object of this invention to provide a method of treating domestic chickens to prevent their developing avian leukosis or diseases etiologically related to avian leukosis.

It is a further object of this invention to provide a method of preventing Marek's disease in domestic chickens by inoculating the chickens with a purified extraction residue fraction of the microorganism Progenitor cryptocides.

It is a further object of this invention to produce a purified extract residue fraction of Progenitor cryptocides, the fraction containing the distinctive antigen of the Progenitor cryptocides which induces the formation of antibodies when injected into a warm-blooded host. "Antibodies," as used here, is intended to mean the specialized proteins genetically programmed to closely fit the antigen that stimulated their production.

Best Mode for Carrying Out the Invention

Evidence for the etiological relationship of Progenitor cryptocides to neoplastic disease has been documented over a period of years, as previously referenced.

Its cultural properties, staining characteristics, and morphology have been fully described. Its filterable bodies have been measured by electron microscope and found similar in size to some viruses. The pathology produced in experimental animals has been reported. It has also been demonstrated in fresh blood samples examined by dark-field and phase microscopy. Also, the production by Progenitor cryptocides in vitro of a parahormone or analog or human chorionic gonadotropin has been described and confirmed by several investigators. See H. Cohen and A. Strampp, "Bacterial Synthesis of Substance Similar to Human Chorionic Gonadotropin," Proc. Soc. Exp. Biol. Med., 152:408-410 (1976); H. F. Acevado, M. Slifkin, G. R. Pouchet and M. Pardo, "Immunohistochemical Localization of a Chorionic gonadotropin-like Protein in Bacteria Isolated from Cancer Patients," Cancer, 41:1217-1229 (1978); L. F. Affronti, L. Grow, R. Brumbough and K. Orton, "Production of Human Gonadotropin-like Substance by Bacterial Tumor Isolates," Alesh. Ann. Meeting Am. Soc. Micro. 1977, p. 84, New Orleans; T. Maruo, H. Cohen and S. S. Koide, "Studies on Choriogonadotropin from a Microorganism", Abst. 951, The Endocrine Society, 61st Annual Meeting, June 13-15, 1979; and P. H. Langè, T. R. Hakala and E. E. Fraley, "Suppression of Antitumor Lymphocyte Mediated Cytotoxicity by Human Chorionic Gonadotropins," J. Urology, 115:95-98 (1976). Progenitor cryptocides is found is practically all warm-blooded animals with cancer. Heavy chemotherapy and/or antibiotic therapy suppress the microorganism, but never destroy it. All isolates used in the studies detailed in this application came from either direct blood cultures or mid-stream urine specimens of human patients. Progenitor cryptocides used in the present invention has the following morphological, cultural and physiological characteristics:

Early culture fast growing:	Short rods and cocci - Gram variable
	Cocci 0.5-0.6 micron diameter, predominantly in clusters, non-motile
Gram reaction:	Gram positive
Ziehl-Neelsen stain:	Variable acid-fast, depending upon amount of mycolic acid present

Coagulase:	Negative
Mannitol:	
Acid aerobically	Positive
Acid anerobically	Negative
Heat-resistant endonucleases:	Positive
Biotin requirement:	Positive
Cell wall:	
Ribitol	Positive
Glycerol	Positive
Mycolic acid	Positive
Acetoin from glucose:	Positive
Chorionic gonadotropin:	Positive (In trypticase soy broth cultures at five days) as determined by pregnancy test kit and RIA
Gelatin stab.:	White surface growth with slow saccate liquefaction
Agar colonies:	Circular, smooth, generally pale, translucent white
Broth containing a fermentable carbohydrate:	Heavy, uniform turbidity with a ring pellicle
Litmus milk:	Acid
Carbohydrate fermentation:	No gas production from any sugar

	Acid Production	Gas Production
glucose	+	-
fructose	+	-
maltose	+	-
sucrose	+	-
trehalose	+	-
glycerol	+	-
galactose	-	-
lactose	+	-
xylose	-	-
arbinose	-	-
raffinose	-	-
inulin	-	-
sorbitol	-	-

Temperature optimum: 37C°

Appearance of Progenitor Cryptocides on Blood Agar Plate:

(1) White discoidal, often hemalytic, with a raised center giving a fried-egg appearance.

(2) Grayish mucoid, often confluent.

(3) Pigmented: occasionally sulfur yellow, sometimes a pink-to-orange variant seen.

(4) Wrinkled intermediate "worm cast," rough, dull, granular with irregular edges, often hemalytic, resembling B. subtilus.

(5) The organism is virulent to mice.

(6) In AJ Broth*, produces a characteristic white rim or soft pellicle.

(7) Sometimes dwarf colonies appear.

Based upon taxonomic studies, Progenitor cryptocides has been identified as an actinomycete. A culture thereof has been placed on deposit with the American Type Culture Collection, and has been assigned No. 31074. Access to the culture is available during pendency of the application under 37 C.F.R. 1.14 and 35 U.S.C. § 122. All restrictions on the availability to the public of the culture deposited will be removed upon granting of the patent.

Progenitor cryptocides is frequently confused with Staphlococcus epidermidis. There is one unique difference in the two organisms. Progenitor cryptocides produces chorionic gonadotropin in vitro, which is not true of Staphlococcus epidermidis. In addition, Progenitor cryptocides has another unique property in that it is intermittently acid-fast. Progenitor cryptocides produces acid from glucose, lactose and maltose in the presence or absence of air.

---

*Alexander-Jackson's broth.
Ingredients:
distilled water - 2000 ml;
beef lung (cut up) - 2 pounds;
peptones - 20 grams: 5 grams each of (a) myosate, (b) gelysate, (c) trypticase, and (d) phytone;
glucose - 10 grams; and
glycerol - 80 ml.
The broth is prepared by boiling the beef lung in water for thirty minutes. It is then filtered through cotton or very coarse paper into a flask containing the other ingredients and the mixture is heated. The crude lung broth can be autoclaved and stored in the icebox and clarified subsequently. It is clarified by depositing a 1-2 mm layer of Infusorial Earth (standard filter cel of Johns-Manville & Company) on a No. 42 Whatman paper disk by laying the disk on a Buchner funnel, applying suction, and then carefully pouring about 500 ml of a 5% suspension of filter cel. After deposition of the layer (when the water goes through clear), the suction flask is rinsed out. The hot medium, as prepared, is then filtered through the prepared disk into the flask. The pH of the medium is adjusted to 7.4 with sodium hydroxide and then tubed into screw-top glass tubes which are autoclaved. The AJ broth is obtainable from the Colorado Serum Company, Denver, Colorado.

Acid is produced from glycerol and manitol only under aerobic conditions. No acid is produced from arabinose, cellobiose, inulin, raffinsoe, rhamnose, salicin, sorbitol or zylose under aerobic or anerobic conditions. Starch and esculin are not hydrolyzed. Growth in broth produces a mucoid deposit. The organism is gram positive in the rod form, but can be variable.

The purified extract-residue fraction of Progenitor cryptocides containing the antigen of the organism is prepared by culturing the organism in a culture media; killing the microorganism; boiling the cells of the microorganism to dissolve the soluble portion of the microorganism, including the cell wall, to release the water-soluble antigen; discarding the heat denatured protein layer, leaving a clear filtrate containing the antigen; precipitating the antigen contained in the filtrate; and separating and purifying the precipitant from the remaining solution. Methanol or, preferably, ethanol or acetone may be used for precipitating the antigen from the remaining solution. Ethanol is preferred. The purified extract residue fraction is redissolved in a physiological saline solution for subcutaneous injection into the warm-blooded host in amounts effective to stimulate an immunological response in the host.

The following examples illustrate the present invention and should not be construed as limiting its scope.

EXAMPLE 1

A sample of Progenitor cryptocides obtained as an isolate from a cancer patient by methods referenced previously was tested for positive production of chorionic gonadotropin-like hormone. The organism was cultured in a liquid media consisting of 17 grams of trypticase soy obtained from the Baltimore Biological Laboratory, Cockeysville, Maryland; 10 grams yeast extract (BBL) and 2.5 grams of K_2HPO_4 per liter. The pH of the liquid media was 7.2. The cultures of the organism were maintained on Mueller-Hinton slants. Overnight growth of the organism was the usual inoculum source. Slants of the organisms were kept in the refrigerator at 5°C for future reference.

250 ml of the above liquid media were put in 500 ml Erlenmeyer flasks. Each flask was inoculated from a single colony from a Mueller-Hinton slant or Mueller-Hinton plate.

Fermentation Conditions. A 20-liter lot of the above trypticase-yeast extract medium was employed in a 20-liter fermenter (New Brunswick Scientific Company, Edison, New Jersey). The temperature of the fermenter was maintained at 37°C, with agitation set at 400 rpm. Sparging of the solution of broth was maintained at a rate of 10 liters of air per minute. The media was sterilized at 15 pounds pressure, 250°F, for 45 minutes, and then cooled and inoculated with an overnight (12 hours) 250 ml shake flask containing the organism. After fermentation for 20 hours, new media was introduced at the rate of 6 liters per hour. The new sterile media was supplemented with 3.5% dextrose. The fermenter was equipped with pH control so that sterile 5N sodium hydroxide could be added on a demand basis to maintain the pH at 7.2.

The harvest pump was set to pump at 6 liters per hour; thus the addition of new media and the harvest rate were set at the log phase of the organism. The harvested culture was centrifuged at 18,000 rpm with a continuous-flow Cepa centrifuge Model Z41. After 120 hours at 28°C, with the air source being a vacuum pump equipped with a glass wool filter previously sterilized, a fresh culture of Progenitor cryptocides was obtained as a paste, 25% solids. The yield was 40 g/l.

The media and the organism were then treated with 0.3% formalin to kill the organism. The media and growth with the added formalin were allowed to stand for several hours at room temperature and then centrifuged in a Sharples centrifuge to collect the dead cells. 200 grams of cells, wet weight, were collected. The dry weight solids of this mass of cells was 24.8% of the wet weight. The cells were adjusted to pH 5.0 with hydrochloric acid and a suspension of the cells in water brought to boiling with constant stirring and allowed to boil for 30 minutes. Upon cooling to room temperature, the mixture was centrifuged and the denatured protein layer was discarded. The remaining clear filtrate, containing the extract residue fraction of Progenitor cryptocides, including the antigen, was treated with 8 l absolute ethanol to precipitate the antigen. A white, water soluble precipitate was obtained which was centrifuged and washed again with absolute ethanol. The precipitate was collected and dissolved in saline solution, 0.9% sodium

chloride containing 0.3% phenol. The final solution contained 1 mg/cc of the alcohol-insoluble material. Analysis of the alcohol-insoluble material indicated that it was a lipopolysaccharide material. The nitrogen content of the material was determined by the micro-Kjeldahl method. Carbohydrate content was estimated by the method of Dubois. This was used in the following animal studies.

Swiss-Webster mice weighing 18-20 grams were purchased from Simonsen Laboratories, Gilroy, California. All of the animals were males. Each group had six to ten animals per group. In most of the animal studies, a Sarcoma 180 obtained from Dr. Chester Stock of Sloan-Kettering Memorial Research Laboratories was used. The tumor was maintained as an ascites by passage weekly in the mice. The inoculum was prepared by aspirating a mouse with a seven-day ascites into a sterile syringe and diluting the cells with sterile saline to obtain a suspension of 1-2 X 10^6 cells per cubic mm. This suspension of cells was used to inoculate the mouse in the left hind leg (hamstring muscle) with 0.1 ml with ascitic tumor suspension. All of the inoculated mice were then placed in a large cage and segregated at random into groups of eight to ten mice. Treatment was started on day one, the day after tumor transplantation, and continued for a total of five days. All of the mice were sacrificed on day fourteen or fifteen, and the weight of the excised tumor determined. The mice were killed by cervical dislocation and the left hind leg removed at the hip joint. The skin was removed to expose the tumor. In many experiments, the right hind leg was also removed in a similar manner and weighed. By subtracting the weight of the normal leg from the tumor leg, the absolute tumor weight was determined. The dose of the purified extract residue fraction is given in the following table. It can be seen that the purified extract residue fraction of Progenitor cryptocides is effective in inhibiting the growth of the mouse tumors. The treated and controlled animals received 0.1 ml doses of respective material intraperitoneally.

Table V

Treatment	No. Experiments	No. Mice	Inhibition Range
Control	5	78	0
0.1 ml (PA) for five days	5	79	65-71

EXAMPLE 2

Sixty eight-week-old leghorn chickens which had been inoculated with 0.5 ml purified extract residue fraction of Progenitor cryptocides, prepared as previously described, were randomly divided into 20 control birds and 40 test birds and housed in cages containing two birds each. The control and test birds were in the same room but were not allowed direct or indirect contact with each other. The birds were allowed free choice of water and feed.

The test birds were inoculated subcutaneously with a cell-associated, highly oncogenic Marek's disease virus and the controls with sterile physiological saline. The seed virus was obtained from Dr. J. M. Sharma, Regional Poultry Research Laboratory, East Lansing, Michigan. The virus was grown in chick embryo fibroblast (CEF) tissue culture, harvested, sealed in five ampules of 0.6 ml each, and frozen in liquid nitrogen. Prior to inoculation of the test birds, the virus was tested for virulence and a titer established in CEF tissue culture as 30×10^4 plaque-forming units per 0.1 ml. At the time of inoculation, each ampule was thawed in ice water and diluted 1:6 in tissue culture medium containing 10% fetal calf serum. Each test bird was then inoculated subcutaneously with 0.2 ml of diluted virus to provide a final inoculation dose of 10,000 PFU/bird (plaque-forming units).

Three weeks post inoculation, 10 of the control birds and 20 of the test birds were necropsied. The remaining 10 controls and 20 test birds were necropsied six weeks post inoculation.

None of the control or test birds died during the test. When necropsied, none of the three- or six-week post inoculated birds or their controls had any gross lesions characteristic of Marek's disease.

In the three-week post exposure group, all of the birds had some lesions suggestive of Marek's virus infection. Twenty-five percent of the test animals had one to three tissues with mild lesions suggestive of exposure to Marek's disease. Seventy-five percent of the birds had lesions in four to six tissues which were compatible with Marek's disease. The control birds had 30% which were free of any evidence of infection with Marek's virus and 70% with mild lesions suggestive of exposure to Marek's virus.

RESULTS: In the six-week post exposure group, all of the birds had some lesions suggestive of Marek's virus infection. The lesions were milder in the six-week post inoculum group, with 9% of the birds having only one to three tissues with mild lesions suggestive of exposure to Marek's virus. Only one bird (5%) had lesions in four tissues which were compatible with a diagnosis of Marek's disease.

DISCUSSION: None of the birds inoculated with a highly oncogenic Marek's disease virus died or developed grossly observable lesions. Microscopic lesions either suggestive of or compatible with infection by Marek's virus were present in all inoculated test birds. The lesions were more prominent in the birds necropsied at three weeks post inoculation, with 25% having mild lesions suggestive of exposure to Marek's virus and 75% having lesions compatible with Marek's disease. In the birds necropsied six weeks post inoculation, 95% had mild lesions suggestive of exposure to Marek's virus and 5% had lesions compatible with a diagnosis of Marek's disease.

The control birds necropsied three weeks following a sham injection had 30% with no lesions and 70% with mild lesions. The controls necropsied at six weeks had 10% with no lesions and 90% with mild lesions.

This test indicates that the birds are protected against exposure to Marek's virus.

EXAMPLE 3

Of 60 five-week-old white leghorn chickens, 30 were vaccinated with two doses (each 0.1 ml) of the purified extract residue fraction of Progenitor cryptocides at two week intervals. Thirty chickens were unvaccinated. All of the birds were raised in wire cages with two birds per cage. The control and test birds were housed in the same room.

The birds were allowed water and feed (Purina Crumbles) ad libitum.

The test and control birds were inoculated subcutaneously with a cell-associated, highly oncogenic Marek's disease virus. The virus was grown in chick embryo fibroblast (CEF) tissue culture, harvested, sealed in five ampules of 0.6 ml each, and frozen in liquid nitrogen. Prior to inoculation of the test birds, the virus was tested for virulence and a titer established in CEF tissue culture as 30×10^4 plaque-forming units per 0.1 ml. At the time of inoculation, each ampule was thawed in ice water and diluted 1:6 in tissue culture medium containing 10% fetal calf serum. Each test bird was then inoculated subcutaneously with 0.2 ml of diluted virus to provide a final inoculation dose of 10,000 PFU/bird (plaque-forming units). The birds were observed daily and the mortalities were recorded.

RESULTS: The birds were observed for a period of six weeks. Post inoculation and mortalities were recorded.

	MORTALITIES	
No. Birds/Group	Vaccinated Group	Non-vaccinated Group
30	1	26

The surviving birds were sacrificed and examined for gross lesions of Marek's disease. All of the chickens appeared to be free of the disease.

	MORTALITIES	
No. Birds/Group	Vaccinated Group	Non-vaccinated Group
30	2	28

The experiment was repeated. The results after six weeks were as follows:

	MORTALITIES		
No. Birds/Group	1 Injection	2 Injections	0 Injection
25	8	4	25

EXAMPLE 4

The antibody response of warm-blooded animals injected intraperitoneally with the purified extract residue of Progenitor cryptocides was subjected to a hemaglutinin

test to determine the effect of the treatment on the antibody response. The tests were performed by standard procedures using the microtiter plate technique. Acceptable hemaglutinin titer for the average mouse ranges from 1:64 to 1:128. A stock culture of Progenitor cryptocides was grown overnight in broth as previously described. Depending upon the number of samples to be run, several tubes were utilized. The broth cultures were centtrifuged and the broth decanted off. The cells were washed twice in PBS and resuspended in PBS to absorbency of approximately 0.75 (0.65 minimum, 0.8 maximum) at 520 mm. 0.05 ml PBS was added to all wells in a "U"-bottom microtiter plate using a standardized pipette. 0.05 ml of serum obtained from the blood of the warm-blooded animals injected with the purified extract residue of Progenitor cryptocides were added to every other well at the head of the column. The serum was diluted with 0.05 ml microdiluter down column. 0.05 ml of cell suspension was added to all wells. All the samples were incubated at room temperature for 30-60 minutes and refrigerated overnight.

Claims

1. A method of preparing a purified extract residue fraction of a microorganism isolated from a warm-blooded animal or malignant tumor of a warm-blooded animal, the microorganism having the capacity to synthesize the polypeptide known as "chorionic gonadotropin" in its total form or in its alpha and beta subunits, comprising:

culturing the microorganism in a culture media,

killing the microorganism,

boiling the mixture containing the microorganism to dissolve the cell wall of the microorganism,

separating the insoluble protein layer from the clear filtrate containing the extract residue fraction,

precipitating the antigen in the extract residue fraction from the remaining filtrate solution, and

dissolving the precipitated antigen in aqueous solution.

2. The method of claim 1 wherein the antigen is precipitated by addition of absolute ethanol.

3. The method of claim 1 wherein the aqueous mixture containing the dead microorganisms is adjusted to pH 5.0 prior to boiling to aid in dissolution of the protein making up the cellular wall of the microorganism.

4. The method of claim 1 wherein the microorganism is Progenitor cryptocides.

5. A purified extract residue fraction for inhibiting the growth of tumors in warm-blooded animals containing as an active ingredient an antigen of a microorganism isolated from a warm-blooded host or host extract carrier of a malignant tumor carrier having the capacity to synthesize the polypeptide hormone known as "chorionic gonadotropin" in its total form or in its alpha and beta subunits, the fraction prepared according to the method of claim 1.

6. The fraction of claim 5 wherein the microorganism is Progenitor cryptocides.

7. A method of stimulating the immune response in a warm-blooded animal by administering to the animal an effective immunostimulating amount of a fraction containing as an active ingredient the antigen residue fraction of a microorganism isolated from a warm-blooded host or malignant tumor of a warm-blooded host, the microorganism having the capacity to synthesize the polypeptide hormone known as "chorionic gonadotropin" in its total form or in its alpha and beta subunits, the extract residue fraction prepared according to the method of claim 1.

8. The method of claim 7 wherein the microorganism is Progenitor cryptocides.

9. A method of inoculating domestic chickens to resist challenge of avian leukosis virus, comprising:

administering a therapeutic amount of a purified extract residue fraction of a microorganism isolated from a warm-blooded host or malignant tumor of a warm-blooded host, the microorganism having the capacity to synthesize the polypeptide hormone known as "chorionic gonadotropin" in its total form or in its alpha and beta subunits, the extract residue fraction prepared according to the method of claim 1.

10. The method of claim 9 wherein the avian leukosis virus is Marek's disease virus.

11. The method of claim 9 wherein the chickens are inoculated with more than one dose of the purified extract residue fraction at spaced time intervals.

12. The method of claim 7 wherein the microorganism is Progenitor cryptocides.

METHOD FOR PREPARING A PURIFIED EXTRACTION RESIDUE FRACTION AND ITS USE IN STIMULATING THE IMMUNE RESPONSE

Abstract

A method is disclosed for preparing a purified extraction residue fraction (antigen) of a microorganism isolated from the blood or urine of a warm-blooded animal or tumor carried by a warm-blooded animal, the microorganism having the capacity to synthesize the polypeptide hormone known as "chorionic gonadotropin" in its total form or in its alpha and beta subunits. The purified extraction residue fraction is an activator and modulator of immunological response and is capable of evoking pronounced prophylactic and therapeutic effects against a variety of tumors in laboratory animals and man. The immune response is stimulated by administering an effective immunostimulating amount of the residue fraction.

Declaration and Power of Attorney

We, Virginia Livingston-Wheeler and John J. Majnarich, declare that we are citizens of the United States of America, residing at 8492 Prestwick Drive, La Jolla, California 92037, and 8541 Southeast 80th Street, Mercer Island, Washington 98040, and having post office addresses of 8492 Prestwick Drive, La Jolla, California 92037, and 8541 Southeast 80th Street, Mercer Island, Washington 98040, respectively; that we have read the foregoing specification and claims, and we verily believe we are the original, first and joint inventors of an invention entitled "METHOD FOR PREPARING A PURIFIED EXTRACTION RESIDUE FRACTION AND ITS USE IN STIMULATING THE IMMUNE RESPONSE," which is described and claimed in the foregoing specification; that this application in part discloses and claims subject matter disclosed in our earlier filed pending application, Serial No. 128,919, filed March 10, 1980, which is a continuation of Serial No. 957,206, filed November 3, 1978, now abandoned; that as to the subject matter of this application which is common to said earlier application, we do not know and do not believe that the same was ever known or used in the United States of America before our invention thereof, or patented or described in any printed publication in any country before our invention thereof or more than one year prior to the filing of said earlier application, or in public use or on sale in the United States of America more than one year prior to the filing of said earlier application; that the common subject matter has not been patented or made the subject of an inventor's certificate issued before the filing of said earlier application in any country foreign to the United States of America on an application filed by us

or our legal representatives or assigns more than twelve months prior to the filing of said earlier application; and that no application for patent or inventor's certificate on said invention has been filed by us or our legal representatives or assigns in any country foreign to the United States of America; that as to the subject matter of this application which is not common to said earlier application, we do not know and do not believe that the same was ever known or used in the United States of America before our invention thereof, or patented or described in any printed publication in any country before our invention thereof or more than one year prior to the filing of this application, or in public use or on sale in the United States of America more than one year prior to the filing of this application, and that the subject matter has not been patented or made the subject of an inventor's certificate issued in any country foreign to the United States of America on an application filed by us or our legal representatives or assigns more than twelve months prior to the filing of this application; and that no application for patent or inventor's certificate on said invention has been filed by us or our legal representatives or assigns in any country foreign to the United States.

We acknowledge our duty to disclose information of which we are aware which is material to the examination of this application.

We hereby appoint RICHARD W. SEED, Registration No. 16,557; BENJAMIN F. BERRY, Registration No. 16,525; KENNETH W. VERNON, Registration No. 23,085; ROBERT J. BAYNHAM, Registration No. 22,816; EDWARD W. BULCHIS, Registration No. 26,847; and JOHN C. HAMMAR, Registration No. 29,928, composing the firm of SEED, BERRY, VERNON & BAYNHAM, 1001 Bank of California