BREAST CANCER:
Immunological Factors Affecting Incidence, Prognosis and Survival

PART I: *Factors affecting host resistance to breast cancer and therefore its incidence and response to treatment*

PART II: *The immunopotentiating effects of concurrent infections, inflammation or fever*

PART III: *Immunotherapy, effects of bacterial vaccines*

Helen Coley Nauts

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February 28, 1984

To Whom It May Concern:

Helen Coley Nauts has written a very scholarly and excellent book discussing all the problems related to diseases of the breast. I have had the opportunity to review the book and find that it is superb. The book will serve many purposes. Its greatest contribution will probably be that of a reference book for any aspect of breast disease that a physician or health provider would seek. It is well written, concise, easy to follow and the material is accurate and it is scientifically sound.

It is a book that can be read from cover to cover and will be especially valuable to students, house staff officers, clinicians and researchers. The format makes it easy to read and it is my opinion that it will have appeal to the nonprofessionals as well as to the professionals. Everyone interested in breast disease, providers of primary care and gynecologists as well as libraries will find this a great addition to their collection. In addition, there are approximately 1,000 references which include classic articles going back many years as well as the most current literature. The completeness of this bibliography list will provide an opportunity to look up and study original material as well as current concepts in breast disease.

I have been greatly impressed by what Helen Coley Nauts has achieved.

It is without any reservations that I recommend this work to you.

Sincerely,

Hugh R. K. Barber, M.D.
Director
Department of Obstetrics and Gynecology

HRKB:mm

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May 27, 1985

Mrs. Helen Coley Nauts
1225 Park Avenue
New York, New York 10128

Dear Mrs. Nauts:

Thank you so much for letting me see a copy of your book on breast cancer. It is really a Herculean effort and I do congratulate you.

You have played an astonishing role in the furtherance of cancer research through your dedication. The cancer research institute owes everything to your enthusiasm and assistance.

Yours sincerely,

Dr. Bearn was formerly Physician-in-Chief at The New York Hospital.

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PART I

Factors Affecting Host Resistance to Breast Cancer and Therefore Its Incidence and Response to Treatment

Introduction

This study analyzes immunological factors affecting incidence, prognosis and survival in breast cancer. It examines and questions some of the basic procedures associated with breast cancer therapy. As Cope noted, "The trouble with training, as distinct from continuing education, is that it keeps one from questioning basic procedures."(168) As Hall recently stated: We rarely consider going back over what is historically accepted as therapeutically effective in cancer. Particularly in surgery and radiation therapy, rarely is any attempt made to find out whether the more radical procedures have definitely proven to be advantageous.(348) A more comprehensive view of breast cancer must be sought in the hope of identifying more effective ways in which to intervene. Surely we are now beyond the time when the diagnosis of breast cancer leads routinely to much the same therapeutic regimen for all patients.(64)

Carcinoma of the breast is the commonest cancer and the leading cause of death from malignant disease among Western women.(837) The prevalence of breast cancer in American women has increased sharply in the past 25 years from 55 per 100,000 to 90 or 95 per 100,000 per annum.(107) Breast cancer was diagnosed in 106,000 women in the United States in 1980.(414) This represents a two-fold increased incidence in the past decade. This is the neoplastic disease with the highest incidence and the greatest mortality.(887) Approximately one out of every 14 women will develop breast cancer during her lifetime. Approximately 38,000 patients will die in 1983 from this most common cancer in women.

Research in cancer of the breast antedates this century and much has been learned, but the effect on survival has not been apparent. Perhaps this is due to the fact that until very recently it has not been recognized that results of treatment appear to be more closely related to the resistance of the host than to the type of treatment. The aggressiveness or indolence of the tumors may thus be related to host factors, rather than just to histologic type and grade of the tumor. As Gordon Taylor stated 30 years ago, we must "remain fearful of any form of treatment or any contingency which may even temporarily undermine the patient's resisting power to deal with residual malignant cells that may have been left behind at operation."(327)

The present study presents pertinent data relating to host resistance of breast cancer and includes all known cases in which complete or partial regression occurred "spontaneously" following concurrent infections, inflammation or fever, (see Part II.) In Part III will be found all cases with microscopic confirmation of diagnosis known to have received immunotherapy, the mixed bacterial vaccines of Streptococcus pyogenes and Serratia marcescens, formerly known as the Coley Toxins, now called Mixed Bacterial Vaccines, (MBV.) This was the first systemic immunoadjuvant to be used on a large number of cancer cases.(602–619) The recent literature on the use of BCG and Corynebacterium parvum as immunoadjuvants is readily available and will only be briefly discussed in this monograph.

When we began our studies of breast cancer over 30 years ago, a patient with a lump in her breast was treated as a semi-emergency. She was taken to the operating room and had a biopsy and frozen section; if the lesion was malignant she was immediately subjected

to a radical or an extended radical mastectomy. After a lengthy hospitalization that physically and psychologically mutilated her, she was discharged by the surgeon, either to the care of a radiotherapist or nobody. She and her husband were assured "we got it all out" and she was told to come back if she ever had any more trouble. Today breast cancer patients are more aware of possible alternatives and traditional procedures are therefore less automatically implemented.

We believe that if modern oncologists will give greater consideration to the importance of all factors which may affect host resistance, they can substantially improve end results and the quality of survival in their breast cancer patients.

Endogenous Factors

GENETIC FACTORS

Certain pedigrees suggest a dominant trait with breast cancer alone or in association with fibrocystic disease of the breast or with other neoplasms such as ovarian or uterine cancer, sarcoma or polyposis and prostate cancer.(15;16;29;67;377;443;500;515–517;759) The Lynchs have made the most exhaustive studies of genetic factors in cancer.(515–517)

Earlier studies have consistently indicated a two to fourfold risk for breast cancer in first degree relatives of breast cancer patients. However, more recently, when patients were classified into presumably more homogeneous groupings based on age of onset, multiplicity of disease, and type of family history, the risks for relatives of some groups of patients increased to higher levels ranging from 9-fold to 51-fold.(16)

Cowden's disease, a cutaneous marker of breast cancer, features facial dermatologic lesions, including pathognomic multiple facial trichilemmonas. These precede the development of malignancy and can identify women with a high risk of developing breast cancer.(100;313)

Anderson's studies at M.D. Anderson Hospital suggest that genetic factors play a much more important role in patients with either premenopausal onset and/or bilateral breast cancer than in patients with either postmenopausal onset and/or unilateral breast cancer. Since women are generally considered to have a 6% chance of developing breast cancer during their life time, these findings indicate that the chances of some women could be higher than 50%, thus constituting an extremely high risk group—the highest yet to be identified in breast cancer. They should obviously be subjected to periodic examinations which should include palpation and mammography. These women are at highest risk between the ages of 20 and 40.(15)

Steinitz et al reported from Israel (1981) four families in which both husband and wife had breast cancer and in one family both father and son had breast cancer.(787) Everson et al reported two families in which infiltrating duct carcinoma of the breast occurred in six men. Preliminary data suggest elevated urinary estrogen excretion in three men from these families, implicating a defect in estrogen production or metabolism in the pathogenesis of male breast neoplasms.(251)

Marks (1981) stated that as much as 10% of all breast cancer in the United States may be associated with genetic factors.(545)

Kelly (1981) noted that not all women with a family history of breast cancer are at high risk of the disease. By assessing whether such cases are premenopausal or post menopausal and unilateral or bilateral, surgeons may more accurately assess a woman's breast cancer risk and be better able to determine appropriate treatment.(443) If the relatives all had postmenopausal unilateral disease, the risk is only 7%, as compared with 50% if the sisters had premenopausal, bilateral breast cancer.

Black et al studied the effect of taking oral contraceptives (OC) on the incidence of breast cancer in patients who had a family history of breast cancer. They concluded that the family history is a significant covariable between OC usage and breast cancer.(67)

Another factor that has not been sufficiently recognized is that a woman's risk of breast cancer may be greatly increased by the presence of other types of cancer in the family.(500)

Individuals at high risk may well be candidates for attempts at preventive immunotherapy by hot baths, injections of microbial vaccines and the use of nutritional supplements designed to stimulate host resistance. They should be encouraged to avoid obesity, to have their children early and to avoid taking anti-inflammatory or immunosuppressive drugs, including antibiotics, except for life threatening infections. Recent studies show that oral contraceptives taken in the third decade protect women against breast cancer by stimulating immunocompetence.

Kelly believes that women whose mothers have had breast cancer constitute a group with special counselling needs. Information about risk need not necessarily engender fear. Her discussion of these needs is very constructive.(442a)

PSYCHIC FACTORS

The possible relation between psychological factors and cancer prevalence has been under consideration for centuries, dating back to Galen and in the 18th century to Guy.(343a;535)

There have been several reports indicating that an increased tendency to breast cancer is associated with specific personality or behaviour patterns or is preceded by a psychological stress. Stress factors include loss, anger, fear, depression and the suppression of these feelings.(696a) *The most consistently reported relevant psychological factor has been the loss of a major relationship through death or separation prior to onset.* After bereavement there is depressed lymphocyte function for weeks.(40) Consequently immunologic incompetence may be both psychogenic and pathogenic. Prior to the onset of their illness, most cancer patients react to personal loss with feelings of extreme helplessness and hopelessness, rather than cathartic grief. Since repression of emotion appears to be a contributing factor in the development of cancer, prevention through psychotherapy might be considered, especially in high risk families.

Recent reports suggest that patients with breast cancer have a greater tendency to abnormal release of emotions as well as extreme suppression of anger, and in patients over 40, extreme suppression of other feelings.(585a) It is possible that chronic suppression of anger could produce widespread metabolic alterations via the hypothalamus and autonomic nervous system resulting in increased secretion of IgA. Serum IgA levels were found to be significantly higher in patients who habitually suppressed anger than in those who were able to express it.(668a)

In patients who have a family history of breast cancer the conscious or unconscious fear of this disease and the suppression of this fear may have an immunosuppressive effect. Persons who are depressed or otherwise emotionally disturbed may deny their troubles and mislead their physicians. These individuals should receive a more comprehensive physical examination than those who are not depressed.

Riley reported on C_3H mice, which normally developed breast cancer. By varying stress factors he could vary the incidence from 2% in low stressed mice to 90% in highly stressed mice. Chronic stress has been shown to increase steroid production, and Riley showed that mouse tumor virus is more carcinogenic in the presence of elevated steroid levels. High steroid levels have been identified as bad prognostic indicators in breast cancer and in lung cancer. Chronic stress inhibits the immune system and increases the susceptibility to disease including cancer.(700)

Stress, mental shock and maladaptation linked with the activity of the stress hormones are not to be ignored in relation to the development of breast cancer. In depression, the plasma cortisol levels are high. Theoretically the growth and spread of breast cancer could be affected by emotional stress and affective disorders, through the hypothalamopituitary pathway. The hypothalamus has widespread connections with the forebrain and limbic system, so that stimuli originating in those regions can modify the release of pituitary secretions. For example, it is known that emotional stress can affect the circulating levels of prolactin, growth hormone, gonadotropin and adrenocorticotropin. Through the hypothalamus, stress might be able to influence the immune response also and therefore through both mechanisms, the growth of breast cancer could be affected.(804) Hypothalamic dysfunction is found particularly in women with advanced breast cancer and in patients with endogenous depression.

Stoll has suggested that there may be a link also between psychological attitudes and the degree of tumor activity in breast cancer. In a retrospective survey those patients showing evidence of metastases in the axilla at the time of presentation or those showing recurrence or metastasis within 12 months of treatment, showed a significantly higher proportion who had received medication for emotional stress in the years before presenting with the tumor.(804)

HORMONAL FACTORS: MENSES, PREGNANCY, LACTATION AND MENOPAUSE

The number of menstrual cycles a woman experiences during her life seems to be a critical factor in the risk of breast cancer. Any event which suppresses menses, such as pregnancy, lactation or artificial menopause helps reduce the risk of breast cancer. This risk is increased in women who have never married, who have never been pregnant, or who have never nursed. The longer a woman lactates, the shorter time she menstruates, the less danger she runs of developing breast cancer.(492) Japanese women, whose breast cancer is only about one-sixth as common as in the United States, menstruate during an average of 21 years and lactate for six or seven years, while women in the Roswell Park Studies menstruated an average of 30.2 years and lactated for only one or two years.

There is a definite relation between the development of breast cancer and the time of the menopause. The incidence of breast cancer in those with late menopause is five times greater than in those with normal menopause.(637;771)

Obese women tend to have a longer reproductive life span, a greater total number of menstrual cycles and greater exposure to a hormonal environment that results in stimulation of the breast and endometrium. In addition the estrogen environment of obese women may be more intense than that of leaner women due to a greater portion of premenopausal cycles deficient in corpus luteum progesterone secretion.(471) It is therefore not surprising that obese women have a higher incidence of breast cancer.

Age at First Childbirth

One of the most significant epidemiological variables related to breast cancer risk is the age at first childbirth, for women having their first pregnancy at age 30 or older have double the risk of developing breast cancer compared to those with first pregnancies a decade sooner. For ductal carcinoma, the risk was highest among nulliparous women and decreased the younger a woman was at the time she gave birth to her first child. The risk

of infiltrating lobular carcinoma, however, was lowest among nulliparous females or those who had given birth at a young age and increased the older a woman was when she had her first child.(505)

A number of studies have reported a higher percentage of breast cancer patients who were never married. Those with breast cancer who did so, married at an older age, waited longer to have the first child and had fewer term pregnancies than those who did not have the disease. Zippin and Petrakis found these differences also were present among a group of breast cancer patients and their sisters.(930)

Cancer of the breast in lactating women is relatively rare, but such women delay in consulting a physician four months longer than non-lactating women. When women develop breast cancer during lactation, the infant immediately rejects the milk from that breast. The frequent practice of assuming that all breast masses in a nursing mother are due to the lactation process should be condemned, especially in cases in which the infant rejects the milk.(323)

A study of unilateral breast feeding and cancer among the "boat people" of Hong Kong revealed that none of these women had cancer *in the breast with which they nursed their children*,(419) i.e. the unused breast is at greater risk.(492)

Cancer During Pregnancy

Concurrent pregnancy has a slight adverse effect on survival in breast cancer up to 10 years after treatment. During the first half of pregnancy, patients may be treated in the conventional manner: a suitable surgical approach without radiation or abortion is preferred. In the last half of pregnancy, the clinically early and less aggressive breast masses may be closely observed and treated in the early postpartum period. If the growth is already Stage III or appears aggressive, the pregnancy should be terminated even before biopsy. *The beneficial effects of a subsequent pregnancy far outweighs the doubtful benefit of prophylactic castration* in the very young patient.(18)

The human and personal aspects of breast cancer treatment as related to pregnancy are specially important in advising the younger age group; should a young patient strongly object to any advised procedure which might interfere with her sense of values, an alternative should, if possible be sought.

From the aspect of breast cancer prevention, early normal pregnancy, i.e., prior to age 21, is of prophylactic significance. The belief that lactation reduces the risk of breast cancer is still widely held despite findings to the contrary in a large international epidemiological study.(534a)

Pregnancy After Mastectomy

The limited information available on this subject indicates that women who become pregnant have no more frequent recurrence of cancer than the expected rate for others of similar age and stage. This is true irrespective of how soon after treatment the pregnancy occurs, and prognosis as regards the cancer is often better than expected.

The risk of recurrence or metastases is greatest in the first two or three years after mastectomy, and a delay of this duration makes it more likely that a woman who is still well will remain healthy after her pregnancy. There is no clear evidence that therapeutic abortion has influenced the development of recurrence in women who have become pregnant after mastectomy. Therefore, abortion is not medically indicated.

ENDOCRINE IMBALANCE

De Waard believes there are *two types* of breast cancer with different etiology. According to his hypothesis most cases of breast cancer occurring at premenopausal age are connected with an endocrine imbalance in which ovarian hormones are involved, whereas in the majority of those occurring after menopause altered hormonal homeostasis are related to overnutrition. (See below, Endogenous Factors, Overnutrition, p. 12)

Excessive estrogen activity, prior to menopause of ovarian origin, after menopause of adrenal origin, has been suggested as the underlying etiological factor in breast cancer. In fact the beneficial effects of adjuvant chemotherapy for breast cancer may result in part from suppression of ovarian function.(713) The production of estrogens in the postmenopausal period may reach a surprisingly high level and the curve of breast stimulation then becomes constant losing its periodicity, particularly when the ovaries show cortical stromal hyperplasia. Jessiman and Moore found urinary estrogen values of 4000 i.u. per 24 hours—40 times higher than expected.(428)

Women undergoing artificial menopause (hysterectomy and bilateral oophorectomy) have a much lower than expected incidence of breast cancer, particularly if castration is done before the age of 37. At least 2,000,000 women in the United States take exogenous estrogens for menopausal or postmenopausal ovarian replacement therapy. There have been only seven reported instances of breast cancer in these women.(253) In a series of 511 women followed for nine or more years who were given long-term estrogen after menopause, there has been a drop in the anticipated incidence of all cancers and no evidence to support a stand that estrogens contribute to the incidence or mortality from breast cancer. The administration of estrogens over a long period of time produces a very real decline in the mortality rate.(109;110)

This evidence indicates that women no longer need to fear using estrogen therapy for menopausal symptoms and to prevent osteoporosis. On the contrary, a growing body of data supports the possibility that the incidence of both uterine and breast cancer may be significantly reduced by long term estrogen replacement therapy. Bakke summarized five such studies.(32) However, in the presence of high risk factors such as family history of breast cancer, benign breast disease or nulliparity, postmenopausal estrogen should be avoided.

In contrast to these effects of estrogen therapy in women, it was observed that prostate cancer patients receiving estrogen therapy may develop mammary cancer, usually bilateral.(519)

Cole and MacMahon believe that a population's breast cancer rate is inversely associated with the urine estriol ratios of its young women.(146;536)

Lemon believed that estriol plays a significant anti-carcinogenic role in women accounting in part for the reduced incidence of breast cancer in Japanese women, in whom low estriol excretion has not yet been reported, and in women with multiple pregnancies in their early child bearing years, or after early castration. Estriol should be an effective form of endocrine therapy for hormone dependent breast cancer.(484)

A recent study in Athens showed that both in follicular and luteal phases of the menstrual cycle, the students aged 15–18 residing in an orphanage, had 50% higher estriol ratios (ratio of the concentration of estriol to the sum of concentrations of estrone and estradiol) as the students at a middle class high school. There was also an indication of less frequent anovular cycles among women with low socioeconomic status.(393) Estrogenic stimulation in the absence of sufficient cyclic progesterone secretion may provide a setting

favorable to the development of breast cancer. Histological changes in the ovary observed in breast cancer patients suggest the existence of hyperestrinism.(771)

Bulbrook et al did a prospective study on the Island of Guernsey between 1961 and 1971 to test the hypothesis that abnormalities in the urinary secretion of androgen and corticosteroid metabolites preceded the clinical appearance of breast cancer. Urine specimens from 4,981 healthy women were collected and it was found that excretion of androgen metabolites was subnormal in 24 of the 27 women who subsequently developed breast cancer. Low levels were found in these 24 women at all ages between 30 to 55 years and could be detected up to nine years before diagnosis.

The excretion of relatively small amounts of androgen metabolites is associated with poor prognosis, and raises the possibility that, as far as growth rates are concerned, the clinical course of the disease may be determined many years before diagnosis. Their findings lend no support to suggestions that low androgen excretion in the established disease is due wholly to "illness" or to active metabolism of steroids by tumor tissues.(107)

Overnutrition and Estrogen: A significant association between body weight and estrogen receptor protein was noted in 83 women with primary and metastatic breast carcinoma: 54% of women weighing over 150 pounds had a low or absent receptor protein vs. 25% of women under 150 pounds, suggesting that in heavier women the endocrine or metabolic milieu favors autonomous growth of breast cancer and that adjuvant therapy should therefore be planned for these women.(650)

The influence of high fat diet on breast cancer risk may be mediated through induced alterations in the fecal steroid levels and the composition of gut bacteria, which may contribute to increased estrogen production.(386) (This is also discussed on p. 41.)

Prolactin

Prolactin is another major hormone implicated in breast cancer. Many investigators believe prolactin is more important than estrogen in mammary tumorigenesis in rodents. Estrogen stimulates prolactin secretion.(761) Elevated serum levels of estrogen and prolactin have been noted in daughters of patients with breast cancer.(375) It is unequivocal that prolactin is an influential hormone in murine mammary tumorigenesis.(892) It appears to participate both in the initiation and promotion steps in mammary cancer. In the initiation phase variations in prolactin secretion appear to influence the metabolism of the mammary epithelium, so that it would be more receptive to or refractory to initiating agents such as chemical or physical carcinogens, or oncogenic viruses, i.e., a permissive action. In the promotion phase, prolactin may either directly or indirectly (via the ovary) stimulate mitotic activity of the "transformed epithelium."(892) The influence of prolactin in human breast tumorigenesis is an extremely important area of research which justifiably is receiving increased attention.

Ben David et al stated "that there may be a higher dependency of breast cancer on prolactin than on steroids. Clinical trials must be carried out to determine the role of 'positive' prolactin receptors in prognosis and prediction." The number of prolactin receptors in the breast tumor specimen will significantly improve the accuracy of predictions made to assess the potential effect of subsequent antiestrogen and/or prolactin suppressor therapy. They suggest that a routine examination of both estrogen and prolactin receptors be made in human breast tumors.(51)

If prolactin is found to influence human breast epithelium in a manner similar to its effect on rodent breast tissue, then prophylactic and/or chemotherapeutic control of human

breast tumorigenesis may be feasible with appropriate drugs to mediate prolactin suppression.(891) In animals other than man prolactin is a stress hormone and there is increasing evidence that physical and emotional stress can produce a moderate (rarely a large) increase in prolactin secretion.(427) (See below section on thyroid as it affects production of prolactin.)

Smedley reported a case of breast cancer in a man who had received cimetidine for three months for peptic ulcer. Bilateral gynecomastia developed. He was also given an antidepressant (doxepin) for a prolonged bereavement reaction after the death of his wife. (As noted above, stress increases prolactin secretion.(761) After being on cimetidine for eight months and doxepin for three months he was found to have a hard malignant mass replacing his right breast. He received radiotherapy and was reported well and free from recurrence 10 months later. Both intravenous cimetidine and tricyclic antidepressants have been associated with benign gynecomastia. This is believed due to raised serum prolactin levels, caused by inhibiting factor and to the anti-androgen effect of cimetidine.

Ergot alkaloids and ergoline derivatives appear to be relatively specific inhibitors for this hormone.(199) They are relatively non-toxic and are effective suppressors of prolactin secretion in all species tested, including man. In a mouse study, only one of 90 mice so treated developed mammary tumors as compared to 24 of 90 controls.(761)

Further study of the effects of life-style and diet on the basal level and stimulated release of prolactin is required to resolve its relationship to breast cancer.(387)

It is well documented that the administration of sex hormones, particularly estrogens, may result in alterations of lymphoid tissue and non-specific as well as specific factors of cellular and humoral immunologic responsiveness.(372)

A number of surveys in the last decade indicate that the use of oral contraceptives does not accelerate the development of cancer, not alter the apparently high risk of breast cancer in nulliparous women or of cervical cancer in promiscuous women of low socio-economic status.

Blaustein et al reported on the association of breast cancer with adenosquamous carcinoma of the endometrium. They found that five of 10 cases in a tumor registry over a 10 year period developed breast cancer. In three it occurred two to three years after hysterectomy. In one case both were discovered simultaneously, and in one case the breast cancer occurred one year prior to the diagnosis of endometrial malignancy. They cited the literature on this subject and suggested that further studies were warranted to determine whether patients with adenosquamous carcinoma of the uterus are at higher risk of developing breast cancer.(71)

Prostaglandins (PGs)

Prostaglandins apparently act as intracellular regulatory molecules that, together with the cyclic adenosine monophosphate (cAMP) systems, govern the response of cells to hormone stimulation. In human cancer patients the capacity of cells to produce prostaglandin increases with the degree of malignancy, i.e. from normal cells to benign lesions to primary tumors, to metastases.(696)

PGs are a group of long chain, unsaturated oxygenated fatty acids. They were first discovered in 1933 and 1935 by Goldblatt in England and Von Euler in Sweden, who found high concentrations in the prostate gland and thus named them prostaglandins. Subsequently it was discovered that PGs could be isolated from virtually any tissue and that they produced a bewildering array of effects in the human and animal body. This family of locally produced powerful hormones orchestrate many of our physiological functions. They are short lived and exist in careful balance.

It was not until 1971 that interest in the PGs heightened when Vane of England's Wellcome Research Laboratories discovered that aspirin works by blocking the body's synthesis of two kinds of PGs.

Tumors can produce material which depresses the immune system and a substantial amount of evidence suggests that PGs are involved. Indomethacin and aspirin which inhibit PG synthetases, can block immunosuppression in vitro and retard tumor growth in vivo. Successful immunotherapy may well depend on our ability to prevent or block the immunosuppressive activity of tumors.(672)

Rolland et al believed that elevated PG production is a marker of high metastatic potential for neoplastic cells.(712)

Prostaglandin Synthesis Inhibitors: *Tamoxifen*, which we discuss on p. 00, is a potent inhibitor of PG synthesis and this factor may contribute to its efficacy in the treatment of breast cancer or its metastases, including the relief of bone pain. Female sex hormones can stimulate PG synthesis.

Flurbiprofen is another PG inhibitor which has been used experimentally and which appeared to prolong survival time in tumor bearing mice.

The improved therapeutic effect when flurbiprofen is combined with radiotherapy and/or chemotherapy indicate that inhibitors of prostaglandin synthesis may be valuable adjuncts to the treatment of cancer.(52;428)

Studies might be undertaken to determine whether women at high risk of breast cancer due to heredity, synthesize more PG than normal.

Note: See below p. 81–82 for discussion of prostacyclin which is *beneficial* in its effects on the breast cancer patient.

In contrast to the effects of estrogen, prolactin and prostaglandins, progesterone and thyroid hormones seem to have an inhibitory effect on breast cancer.

Progesterone

This hormone is produced by the corpora lutea, adrenal cortex and placenta. Its significance in breast cancer incidence is only now being recognized.

Cowan et al found that patients with progesterone deficiency had 5.4 times the risk of premenopausal breast cancer compared to women with the nonhormonal (NH) causes of infertility. Women in the PD group also experienced a 10-fold increase in deaths from all malignant neoplasms compared to the NH group. The incidence of postmenopausal breast cancer did not differ significantly between the two groups.(171)

Recently Pichon et al reported a very low frequency of remote metastases in progesterone receptor-positive breast cancers which was inversely related to progesterone receptor concentration. The close correlation between plasminogen activating activity (PAA) and progesterone receptor in human breast cancer cytosol would seem to indicate a causal relationship between fibrinolytic activity and metastatic potential in these tumors.(670)

Thyroid Function

The high incidence of breast cancer in countries where there is a high incidence of goiter is not coincidental, but evidence of an important linkage. Experimental work suggests that thyroid activity and its regulation has a bearing on neoplasia, especially breast cancer. In Japan and Iceland, there is a low incidence of endemic and non-toxic goiter and a low incidence of breast cancer, while in Mexico and Thailand, there is a high incidence of goiter and of breast cancer.(282) Iodine appears to be a prerequisite for the normalcy of breast tissue.(246) When iodine is lacking, the parenchyma in rodents

and humans show atypia, dysplasia and even neoplasia. Iodine-deficient breast tissues are also more susceptible to carcinogen action and promote lesions earlier and in greater profusion. Metabolically iodine deficient breasts show changes in RNA/DNA ratios, estrogen receptor proteins and cytosol iodine levels. Iodine appears to be a compulsory element for breast tissue growth and development. It presents great potential for its use in research directed toward prevention, diagnosis and treatment of breast cancer.

Mittra et al have postulated that suboptimal levels of circulating thyroid hormones may abnormally sensitize mammary epithelial cells to prolactin stimulation, which may lead to eventual neoplasia.(576) Certainly once breast cancer has developed, patients with a history of hypothyroid disorders have a much more rapid recurrence rate after mastectomy, together with a poorer survival experience than euthyroid or hyperthyroid women.(583)

It has been suggested that the much lower incidence of breast cancer in Japanese women compared to American or British women may be due to the high thyroid activity in the Japanese.(827) Diminished thyroid function may be a predisposing factor to breast cancer in Japanese women.(827)

In a hypothyroid state, a higher level of estradiol is maintained. When a patient is brought to a euthyroid state, there is a relatively greater conversion to estriol or less active estrogen.(282) Several published reports now suggest that failure to adequately treat hypothryoidism, goiters or thyroiditis with thyroxin leads to enhanced development of breast cancer in susceptible persons.(485)

Hypothyroid women with metastases show a significantly lower survival time.(26) Thyroid function is significantly lower in patients with blood-borne metastases than in those with localized disease.(229) It is important to note that there is a ten times greater incidence of thyroid disease in breast cancer patients.(697)

The more thyroid there is in the blood, the higher the histamine content in cells, the lower the level of lipids, the less tendency there is to cancer. Histamine activates the RES. A few physicians have administered thyroid (1–5 gr. daily) for years as a prophylactic to prevent recurrence, with apparent benefit.(225;507) An earlier report noted that a recurrent breast carcinoma entirely disappeared under persistent use of thyroid extract for 18 months.(646)

Oral doses of triiodothyronine given concomitantly with radiotherapy markedly increased the sensitivity of tumors to radiation.(786)

Since thyroid output in both rats and humans is reduced in the immediate postoperative period, it would seem beneficial to administer small doses of thyroid before and after surgery to breast cancer patients.

Geographic differences in the rates of breast, endometrial and ovarian cancer appear to be inversely related with dietary iodine intake. Endocrinological considerations suggest that a low dietary iodine intake may produce a state of increased effective gonadotropin stimulation, which in turn may produce a hyperestrogenic state characterized by a high production of estrone and estradiol and a relatively low estriol to estrone plus estradiol ratio. This altered endocrine state may increase the risk of breast, endometrial and ovarian cancer. Increasing iodine intake may reduce the risk of these cancers.

Hyperthyroidism was induced in mice by adding 5,000 or 10,000 parts per million of thyroid powder to their diet. Sarcoma 180 was implanted after 12 to 16 days of thyroid ingestion. Nine or ten days later the tumors (except in one group of males) were all significantly smaller than in the controls.(903)

Spontaneous mammary cancer can be prevented in mice by the administration of the thyrotropic hormone of the anterior pituitary gland. This hormone in some respects is a physiological antagonist to the estrogenic hormone.

The above data suggest that the thyroid function of breast cancer patients should be determined prior to therapy and that they should be given thyroid in order to increase their resistance and help potentiate their response to whatever therapy is given.

Thymus

The role of the thymus in the etiology of human breast cancer is not known, but evidence exists for a high incidence of this tumor in diseases in which thymic germinal centers or thymomas are common, such as myasthenia gravis. Such patients have increased frequency of bilaterality. Thymectomy exerts a protective effect. This procedure causes a considerable increase in immunocompetence. The mechanism operating in the prevention of breast cancer in experimental animals by thymectomy may also be operative in man. In both instances the endocrine function of glands other than the thymus may be involved. There is a need for a more detailed study of this possibility.(648)

FUNCTIONAL CAPACITY OF THE LYMPHATIC TISSUES

Halsted was one of the first to note that a certain proliferative reaction of the axillary lymph nodes of breast cancer patients was associated with markedly prolonged survival.(353)

There appears to be a positive association between patient survival after surgery and the extent to which the sinusoids of the axillary lymph nodes are distended by elongated histiocytes (sinus histiocytosis). It is thought to be a morphological manifestation of cell mediated immunity directed against cancer.(69) Berg noted that breast cancer with lymphatic infiltrates had fewer node metastases, less involvement of the apex of the axilla and, when metastases were present, a higher cure rate.(55)

The presence of bilaterally palpable axillary lymph nodes was found to be a prognostically favorable clinical sign. The superior survival of such patients was most closely correlated with increased sinus histiocytosis reactivity of the homolateral lymph nodes.(66) These data suggest that bilateral palpable nodes may be a manifestation of a host defensive response.(185) Japanese women show significantly more lymphatic infiltration around invasive mammary carcinoma than women in New York, confirming previous studies, a finding suggestive of greater host resistance to breast cancer among Japanese women.(131)

Crile's group in Cleveland studied the role of regional axillary node lymphocytes in the immune response to tumor cells in breast cancer patients. They found that patients who had no nodal or other metastatic involvement showed a significant tumor cell–lymphocyte reaction in vitro; while those who had extensive involvement of the axillary nodes showed no interaction. In six patients with no nodal involvement both the nodal lymphocytes and the peripheral lymphocytes were available for studying the interaction with tumor cells. In all of these, the nodal showed a greater degree of reaction than the peripheral lymphocytes.(177) This finding suggests that removal of the axillary nodes may deprive the patient of an important immunological defense. Instead we should stimulate them to greater reactivity by regional injections of bacterial vaccines.(602–619)

Others have noted that breast cancer prognosis is better in women who, before treatment, have an increased number of circulating lymphocytes.(699) Gatch and Culbertson stated: "The good results after some radical operations are due to tissue resistance to cancer growth and not the removal of every bit of cancer . . . progressively more favorable groups come for operation. Earlier operation, however, has not decreased the death rate of breast cancer."(311)

Ellis' studies support the concept that regional lymph nodes in breast cancer are immunologically competent, and that the lymphocytes in these nodes are more reactive to tumor antigen than are the circulating lymphocytes.(242)

In addition to removing or destroying these important cells, by radical surgery or irradiation, these procedures also have a deleterious effect because of their depressant action on the reticuloendothelial system. Several recent studies, such as those of Stjernswärd, have shown that *irradiation for breast carcinoma leads to a long lasting lymphopenia* (mainly T cells). This effect may be relevant to the development of distant metastases.(796–800)

Hamlin produced convincing evidence that the prognosis in breast cancer is dependent on the host's reaction to the tumor as judged by the number of lymphocytes and plasma cells surrounding the tumor and presence of a marked reactive hyperplasia in the draining nodes.(358)

He noted that the depressant effect of radiation on the function of the lymphoid system and circulating lymphocytes has been known almost since irradiation was first used. Therefore, the consistently poorer survival of breast cancer patients receiving postoperative radiation may be due to the immunosuppressive effect of the irradiation.(188) Bond reported that the postoperative irradiation does not increase the survival time of patients with nodal metastases and may, in fact, shorten the survival period of those without nodal metastases.(89)

The Fishers noted in 1967 that lymph nodes are not the effective obstacles to tumor cell dissemination that they have been assumed to be.(266) All regional lymph nodes in patients with breast cancer are not biologically similar. Thus, the reason why some regional lymph nodes contain metastases and others do not is more likely due to biological differences than because of chance anatomical transport to some nodes and not to others.(269) It would be of interest to see if bacterial vaccine injections could affect the migration-enhancing factor.

Fisher has undertaken very extensive studies concerning the regional lymph nodes in cancer.(260;267;267a;269;274;275;278) In 1974 he suggested that high axillary nodes in breast cancer patients are more closely related functionally to distant, rather than to low axillary nodes and that despite their anatomical location, they might best be considered biologically and relative to their surgical management in the same category as supraclavicular, cervical or contralateral axillary nodes. Fisher believed that in view of the increased uptake of tritiated thymidine by *low* regional lymph nodes, reflecting the possible consequences of stimulation by tumor antigen, the wisdom of removing these low axillary nodes in breast cancer operations may be challenged.(274)

In this connection, Tee and Pettingale note that there is considerable evidence that the regional nodes are involved in a specific anti-tumor immune response. Thus, *the removal of these nodes together with the tumor might significantly deplete the number of cells capable of reacting against the tumor in the future.*(820)

Gewant and Goldenberg at Yale have studied the interrelations between lymph nodes and breast carcinoma and they concluded that axillary lymph nodes may contain elements which inhibit primary growth and excision of such nodes as part of primary surgical therapy for breast cancer may be inappropriate.(315a)

Baum and Edwards, reporting on the "Watch Policy Group" study in England,(44) stated that the fact that in this trial, the great majority of palpable nodes regress following simple mastectomy, Stage II reverting to Stage I, highlights the dilemma as to the prognostic significance of such nodes and how to treat them.

There is evidence that enlargement in about one-third of these lymph nodes is due to sinus histiocytosis.(69) It may be that a proportion of the nodes which undergo spontaneous

regression do so because of the removal of the tumor and the consequent stimulus to the sinus histiocytosis. Radiotherapy, as it has been traditionally employed following simple mastectomy, not only interferes with the function of the regional lymph nodes, but also with other aspects of the reticuloendothelial system and if this is so, then routine post-operative radiotherapy to regional nodes may be harmful.(69)

Fisher's studies indicate that virtually all regional lymph nodes (with or without metastases) from patients with primary operable breast and colon cancers contain cells capable of responding to PHA stimulation. If, as is generally considered, such a response is indicative of lymphocyte immunocompetence, then regional lymph nodes continue to possess immunologic capabilities despite the presence of growing tumors.(259–278) Further studies indicate that *cytotoxicity by cells from nodes regional to a primary tumor is unique*. Following removal of the primary tumor, cells from regional lymph nodes rapidly lose their cytotoxicity. In contrast, cells from non-regional lymph nodes demonstrated increased cytotoxicity at any time following removal of the primary tumor when exposed to a second focus. These findings have relevance to the site of administration of immunotherapy. Perhaps such therapy begun prior to surgery can prevent loss of cytotoxicity of the regional lymph node cells.

Indications that immune mechanisms have an important function in the breast cancer patient's resistance to her disease have challenged the standard surgical procedure of en bloc excision of the tumor and its regional lymph nodes as the initial therapy for early breast cancer.(845) One must consider the relative risk of leaving residual disease in the axilla versus the possibility of lowering the host defense against tumor by removing uninvolved regional lymph nodes.(177)

Forrest (1978) noted that removal of uninvolved lymph nodes cannot be beneficial and may do harm. There is now good evidence from controlled randomized studies in two common cancers, breast cancer and malignant melanoma. These studies show that prophylactic resection of nodes believed *not* to be involved has no more influence on the prognosis than waiting until their progressive enlargement indicates the need for treatment. As this occurs in a minority of patients whose regional lymph nodes are not clinically or pathologically involved at the time of primary surgery, much morbidity would be spared if these uninvolved nodes were not removed.(286;287)

A recent *in vitro* study of axillary lymph node cells from breast cancer patients showed that patients over 60 years of age had significantly lower percentages of T lymphocytes and higher percentages of B cells, as compared with patients 45 years or younger. Similarly the response to PHA was lower in the older patients. Thus, elderly breast cancer patients are similar to normal elderly people who generally show a marked waning of cell mediated responses.(395)

The gradual decrease in immunoreactivity in older patients is now well recognized. The difference is particularly significant between women less than 45 and those over 60 years of age. There is a drop in the hyperplasia index in the critical years 45 to 49 years.(893;894) These findings might be an indication of a direct link between ovarian hormones, probably progesterone, and immunity and it would challenge the concept of oophorectomy performed as a prophylactic measure in premenopausal patients.(893)

BENIGN OR PRECANCEROUS LESIONS

Benign breast disease is well known as one of the very important factors increasing the risk of breast cancer. It may be considered an important evolutionary link between

the normal mammary gland and carcinoma. The recent progress made in hormonal investigation—particularly accurate plasma steroid measurement and detection of steroid receptors in breast tissue—have provided valuable information. These data lead to the conclusion that the different clinical expressions of this disease are due to an ovarian dysfunction. Evidence for this was found in an investigation of 184 patients with various benign breast diseases (permanent mastodynia, fibroadenomas, cystic mastitis and fibrocystic disease.) In all these patients the luteal phase progesterone to estradiol ratio was found to be significantly lower than in normal women. . . . These findings prove that benign breast diseases are hormone dependent at least as regards recent lesions. It is postulated that they can be induced by an unopposed estrogen effect due mainly to an inadequate luteal function.

A study in Paris included 500 patients with benign breast disease treated by progesterone and progestins in order to correct their local and systemic hormonal insufficiency. The best clinical results were obtained in young women with recent lesions.(555a) There is no direct proof that the same hormonal environment plays a major role in the development of breast cancer. There is only indirect evidence that leads one to consider the defect of corpus luteum progesterone secretion as a common risk factor for development of both benign breast disease and cancer. It is only by the early and long term treatment with progesterone and progestins of a large cohort of women either with benign breast diseases or with high risk of breast cancer that an answer to such an hypothesis will be given.(555a)

There appears to be a two to three fold increased incidence of breast cancer in patients who have had benign breast disease.

Fibrocystic Disease or Mammary Dysplasia

Fibrocystic disease or mammary dysplasia is the commonest abnormality of the female breast involving up to 50% of women during their lifetime.(774) Usually multiple small cysts are embedded in breast tissue affected by varying degrees of fibrosis where it forms a localized thickening or general lumpiness of the breast. Symptoms are frequently exacerbated before or with the menses. At any time one or several cysts may suddenly enlarge to form a mass. Clinically, this presents as a discrete lump in the breast which is usually smooth, mobile and firm, but if surrounded by an area of gross fibrocystic disease may be ill-defined and integrated into surrounding breast tissue where it may simulate a scirrhus carcinoma. (See p. 114 for beneficial effects of Vitamin E for fibrocystic disease.)

Diagnosis

The most common cause of breast pain is fibrocystic disease. The pain is cyclic, increasing in the premenstrual phase with an associated fullness of the breast.(249) It is usually bilateral, although often more pronounced on one side and more marked in the upper, outer portions of the breast. The diagnosis usually presents no dilemma. The explanation for cyclic breast pain appears to be a hormonal imbalance, possibly including consistently higher prolactin levels than in control subjects. (See below for beneficial effects of thyroid extracts for breast pain due to fibrocystic disease.)

Though many surgeons still prefer to excise a localized cyst and safeguard the patient against the possibility of an underlying cancer, an increasing number since 1953 are treating cysts by simple aspiration. Forrest et al describe their procedure: Should the mass prove to be solid, excision biopsy is clearly indicated.(288) Should it be cystic, it is

aspirated to dryness. The color varies from pale amber or clear to dark green. The fluid is sent for cytological examination. (Lesnick states that if cyst fluid is not bloody, cytology is not necessary since the fluid is acellular.)(487) Bilateral mammography or xerogram is arranged by Forrest who reviews these patients three weeks later. The breast is carefully examined for refilling of the cyst or for other palpable masses and the findings recorded. Indications for excision biopsy are: a) a palpable mass at the site of the cyst; b) and abnormal mammogram or xerogram; or c) blood or abnormal cells in the cyst fluid. If none of these are present, no further treatment is given, but the patients are followed periodically, those under 40 for six months, those over 40 indefinitely. This policy is safe, economical and reassuring to the patient.(288) Lesnick warns that every cyst should be aspirated to determine its nature since the nodule thought to be another cyst and left untreated too often turns out to be a carcinoma.(487)

Medical Treatments

Diuretics: Symptoms are frequently exacerbated before or during the menses. This is commonly believed to be due to increased body water in the luteal phase of the cycle, and for this reason diuretics have been widely used to decrease these symptoms, *but these seem to be of limited value*.(509) Progesterone, the luteal phase hormone, actually is a natriuretic or salt-losing hormone. Dimethyl sulfoxide was reported to benefit 80% of 122 patients in a double-blind study in Germany.(Cited by 509)

Thyroid Hormone: There seems to be a correlation between hypothyroidism and mammary dysplasia. Thyroid hormone therapy has provided improvement of cystic mastitis in 286 patients with clincial or subclinical hypothyroidism.(190) Several Russian oncologists have used iodine-containing drugs with varying success.(Cited by 509) Investigation of thyroid function of patients with mammary dysplasia should be included in their initial evaluation. Thyroid extract or levothyroxine (Synthroid) reduces breast pain and breast nodularity in patients with mastodynia due to fibrocystic disease. Estes noted rapid pain relief in 73% of his patients with total relief in 47% after daily treatment of 0.1 mg. of levothyroxine.(249)

Steroids: Almost every type of steroid hormone has been tried in these patients. A major breakthrough occurred with the development and approval of danozol (Danocrine) for treatment of this condition. Comprehensive studies in Europe and the United States have shown a response rate of 93% on 200 mg/day for four to six months. The incidence and severity of side effects was low. The overall response rates were: relief of pain (97%); relief of tenderness (90.5%); and decrease in nodularity (73%). This is an effective treatment for symptomatic patients and has a long term effect in resolution of the disease process. The recommended dose is 100 to 400 mg/day for two to six months, depending on disease severity and patient response.(542)

Tamoxifen: Tamoxifen is a synthetic anti-estrogen compound that competes with estradiol for estrogen receptors in target tissues and lowers serum prolactin levels. It has been used successfully to treat patients with severe mammary dysplasia:(698a) 71% of 63 patients had complete remission of symptoms and disappearance of lesions with no recurrence in all but two of the responding cases.

Bromocriptine: This compound is a dopamine agonist and prolactin inhibitor. It has proved effective in producing improvement in a small group of cases with severe mammary dysplasia.(509)

Vitamins: Since World War II when gynecomastia in captured soldiers was responsive to *Vitamin B_1 therapy*, oral B_1 has been used to treat patients with mammary dysplasia. The rationale being that Vitamin B_1 is necessary for hepatic metabolism of estrogens, and excessive estrogens may cause mammary dysplasia.

Vitamin E has been used in these patients since 1965 by several oncologists with a clinical response rate of 75 to 85%.(509;774) The dose used was 600 units daily for two menstrual cycles and this caused no significant side effects. London et al reported that this treatment may correct an abnormal progesterone/estradiol ratio in patients with mammary dysplasia, with implications for reducing future risk of breast malignancy.(509)

Abstinence from Methylxanthines: Minton recently reported that in women with clinically detectable fibrocystic disease of the breast about two-thirds of benign breast lumps disappear in those who completely eliminate all forms of methylxanthines, i.e. caffeine, theophylline and theobromine.(575) Aminophylline, a common asthma medication, may also cause breast pain.

On an average, women with benign breast disease were found to consume a cup of coffee or tea several times throughout the day, thus maintaining a steady level of methylxanthines. Minton advised a group of women with breast lumps to stop methylxanthine consumption and cigarette smoking. Complete resolution of the lesions occurred in 65% of those who did, within two to six months as shown by physical examination, mammogram and echogram.

Most women who resumed drinking coffee or other proscribed beverages had regrowth of the lumps. Since methylxanthine consumption is widespread, and only about 50% of women have benign breast disease, a differential sensitivity to these chemicals undoubtedly exists, but for women with a family history of breast disease, including cancer, it may be wise to eliminate methylxanthines completely.(575)

Heyden does not believe that Minton's study was sound.(383) Perhaps a more carefully planned protocol on a larger number of cases is warranted. A study of the Mormon population as regards the incidence of fibrocystic disease might yield further data as they do not drink coffee or tea.

Ernster et al (1982) reported on a small randomized study of the effects of a caffeine-free diet on benign breast disease.(244) They found a statistically significant reduction in clinically palpable breast findings in the abstaining group as compared with controls but the absolute change was minor.

A larger study by Brooks et al (1981) dramatically showed the improvement of fibrocytic breast disease with restriction of methylxanthines, coffee, tea, colas, chocolate, theophylline-like drugs and caffeine-containing over-the-counter medications' ingestion. They demonstrated that the graphic stress telethermometry system affords a precise method of monitoring breast disease and detecting progression or regression of breast abnormalities.(99a)

Bard has observed marked disappearance of fibrocytic disease in such patients examined before and after abstention from caffeine etc. as seen with ultrasound.(122)

London's Suggested Approaches to Therapy, 1982: After a diagnosis of mammary dysplasia is made and malignancy is excluded by examination, aspiration or incisional

biopsy, thermography, mammography etc., London starts administering Vitamin E (d-tocopheral acetate), 600 IU/day for two menstrual cycles. If reexamination suggests objective improvement, this is continued for a total of six months.

In patients with severe symptoms who do not respond to Vitamin E, London regards danozol as the next therapy of choice. Due to the cost and response rate, doses of 100 to 200 mg/day should be used for four to six months. Patients should be advised to use nonsteroidal contraception during therapy.(509) Patients with severe symptomology who do not respond to this regimen may then be given tamoxifen or parlodel when these drugs are approved for use in fibrocystic disease.

Finally, an informed patient, as well as an open patient-physician relationship encourages the close follow-up these patients require.(509)

BREAST CANCER: HISTOLOGICAL TYPES AS REGARDS TUMOR GROWTH POTENTIAL OR VIRULENCE

Prognosis can be influenced by the histological type of cancer and whether it is invasive; by its grading or degree of differentiation; by its doubling time; growth pattern and margins; and length of disease-free survival; and whether there is lymphatic or blood vessel invasion. Of these the *histological pattern and grade of the cancer are the most important*, and are discussed here.

Histology

1. Paget's disease of the nipple and areola. (This lesion and primary malignant melanoma may look much alike.)
2. Carcinoma of mammary ducts
   Non-infiltrating
   a) Papillary carcinoma
   b) Comedocarcinoma (without stromal invasion)
   Infiltrating
   c) Papillary carcinoma
   d) Comedocarcinoma
   e) Carcinoma with fibrosis (scirrhous carcinoma)
   f) Medullary carcinoma with lymphoid infiltration
   g) Colloid carcinoma
3. Carcinoma of lobules
   a) Noninfiltrating (carcinoma in situ)
   b) Infiltrating
4. Relatively rare carcinomas
   a) So called "sweat gland" carcinoma
   b) Intracystic carcinoma
   c) Inflammatory carcinoma (1 to 4% of all breast cancers)
   d) Adenoid cystic carcinoma
   e) Squamous cell carcinoma
   f) Spindle cell carcinoma
   g) Carcinoma with osseous and cartilaginous metaplasia
   h) Carcinosarcomas

5. Sarcomas
   a) Cystosarcoma phyllodes
   b) Hemangiosarcoma
   c) Stromal sarcoma
   d) Sarcomas of mammary stromal origin comprise the non-epithelial malignant neoplasms of the breast.
6. Reticuloendothelial neoplasms of the breast are somewhat more common. They may appear initially as breast masses and can be confused with medullary carcinoma with lymphoid stroma.

Prognosis

The following *non-invasive* breast cancers have an excellent prognosis approaching 100%: lobular carcinoma in situ, intraductal (comedo) carcinoma without stromal invasion, Paget's carcinoma confined to the nipple and areola, and non-invasive papillary and intracystic carcinoma.

Certain *invasive* histologic types also carry a good prognosis: adenocystic, colloid (gelatinous or mucinous), comedo with minimal stromal invasion, medullary with infiltrate, papillary, and tubular.

Histologic Grading

Greenough (1925) developed a technique for grading mammary cancers. He divided tumors into three grades based on structural differentiation: Grade 1, well differentiated; Grade 2, moderately differentiated; Grade 3, undifferentiated. This grading was reviewed by Bloom in 1950,(74) and in 1956, he showed a close correlation between survival time and the tumor grade.(75) Others such as Fisher et al have found that Grade 1, well differentiated tumors are correlated with older women, absence of nodal involvement, and histologic types associated with a good prognosis.

Black et al have recently emphasized the importance of nuclear rather than general grading in evaluating the degree of anaplasia of a breast carcinoma. They reported a positive association between patient survival and the degree of nuclear differentiation of the primary lesion. Cutler et al (1963) had also reported a definite correlation between nuclear grades and patient survival. The system is outlined as follows:

Grade 1. Nuclei showing marked variations in size and shape, prominent nucleoli, chromatin clumping and numerous mitotic figures (undifferentiated.)

Grade 2. Nuclei whose appearance (moderately differentiated) is intermediate between the two extremes of Grade 1 and 3.

Grade 3. Nuclei that are quite similar in size and appearance to those of the homologous noncancerous cells.

Exogenous Factors

RADIATION

High risk of breast cancer is said to be associated with genetic factors, pre-existing breast disease, artificial menopause, family history of breast cancer, older age at time of first pregnancy, high socioeconomic status, specific blood groups, fatty diet, obesity and hormonal imbalances. *But none of these factors is as certain to cause cancer of the breast as ionizing radiation.*(757;758)

In recent years there has been a greater awareness of the carcinogenic or immunosuppressive effects of radiation as it relates to breast cancer development or progression.

The three tissues most apt to develop cancer following exposure to radiation are the breast, thyroid and the bone marrow. Age at exposure is perhaps the most important host factor influencing subsequent cancer risk.(82) Solid tumors have a minimum latent period of about 10 years.

Women who received repeated fluoroscopies for tuberculosis had a higher than expected incidence of breast carcinoma in later years.(82;83;195;534;601;875) The many reports on the increased incidence of breast cancer among the women of Hiroshima and Nagasaki are now well known.(471;472;869) It has also developed in women receiving x-rays for postpartum mastitis.(471;508;559;892) Women who have received breast radiation who develop benign breast disease, particularly cystic disease, are at a high risk for breast cancer and should be carefully monitored. Women who were irradiated at the time of their first childbirth are at especially high risk of breast cancer.(748;913)

Two sisters with a family history of breast cancer developed Hodgkin's disease which was treated by radiation. The breast tissues received several hundred rad of scatter radiation during this therapy. One sister developed breast cancer four years later, the other 11 years later. Development of this second primary in these sisters apparently resulted from the combination of both the genetic factors and the carcinogenic effect of the radiation.(499) Gardais and Poncheville reported two cases of Hodgkin's personally observed in whom breast cancer developed seven years later following radiation therapy. They also thoroughly reviewed the literature.(306)

In two women who had undergone radiation of the immature breast, at the age of a year, the other at 11 years, carcinoma of the hypoplastic breast developed at the age of 28 and 27 years. The first was irradiated for a birthmark adjacent to the nipple. The other for lymphoma of the mediastinum (3760r). This patient died of sarcoidosis following thoracotomy 12 years after onset of the breast carcinoma. The other patient remained free from disease eight years after mastectomy.(418)

Carcinoma of the male breast can occur many years after radiation therapy for prepubertal gynecomastia.(512)

Female radium watch dial painters first employed before 1930 were found to have had a significant excess of breast cancer incidence and mortality, only among those with a radium intake of 50 u Cl or greater.(5)

More recent concern has been directed toward the indiscriminate use of mammography for diagnosis of breast diseases. Mammography is not the perfect answer to early detection because it is tedious and expensive and misses perhaps 15% of the cancers. It is especially inaccurate in young breasts. The consensus of opinion now is that women under 50 should not be given mammography unless they are at high risk of developing breast cancer due to genetic or other predisposing factors.(753)

Postoperative radiation therapy of a primary breast cancer led to development of a cutaneous angiosarcoma in the mastectomy scar 12 cm. in diameter when diagnosed. Death occurred 13 months later despite chemotherapy.(354)

IMMUNOSUPPRESSION

Due to Immunosuppressive Drugs

The literature concerning malignancies which develop following immunosuppressive drugs is now very extensive.(230;232) This fact was made specially apparent from the cases collected by Penn among recipients of organ transplants.(661)

We must now recognize that immune responses are important in cancer patients, and that many of the therapeutic procedures used may have a deleterious effect because of their immunosuppressive effects on the reticuloendothelial system and other immune defenses. Such agents include radical surgery, some cytotoxic drugs, and radiation. Several recent series indicate that less morbidity and better end results occur in breast cancer patients *not* given routine radiotherapy following radical surgery.(89;101;114;145;170;188;276;433;523;656;719;795–800) (For further discussion of the immunosuppressive effects of these modalities see sections on radical surgery, radiation and chemotherapy.)

Cortisone, butazolidin or other drugs of this type appear to have been responsible for the development, reactivation or metastatic spread of many types of cancer.(439) In one study of breast cancer patients, metastases involving the mucosa and submucosa of the stomach and duodenum were seen in 26 patients and were positively correlated with the use of adrenal steroid therapy. They were six times as frequent in the adrenal steroid treated group as in the control group. The patient with carcinoma of the breast receiving adrenal steroids who develops signs of a bleeding ulcer has an even chance that there will be breast carcinoma at the site of ulceration. Patients so treated also had significant increase in metastases to the lungs, liver, heart, opposite breast, brain and spleen when compared to control patients with disseminated breast carcinoma not receiving adrenal steroids.(744) Patients who had undergone hypophysectomy or adrenalectomy or both and who were receiving replacement adrenal steroids, had a significant increase only in splenic metastases.(744)

The fact that relatively low physiological doses of aspirin can inhibit lymphocyte transformation is not well known. One action of aspirin may be to turn off the immune response of lymphocytes. Some patients may have cells which are suppressed by low doses of aspirin, others require high doses.(635)

These findings suggest that physicians should not use adrenal steroids, aspirin or other anti-inflammatory drugs in patients with a family or prior history of breast cancer, in order to avoid their immunosuppressive effects in patients at higher risk of developing or reactivating a neoplasm.

The administration of immunosuppressive treatments should now be accompanied by some form of immunotherapy designed to stimulate the reticuloendothelial system, activate macrophages and protect or restore the hematopoietic tissues. This seems to have occurred in patients treated by bacterial vaccines or in whom an acute bacterial infection developed. (See cases cited in Part II and Part III.)

Until recently very little was known about the effect of virus infections on the function of the immune system.(633) Information emerging from recent studies suggests that viral infections may suppress immune competence and thus be a factor in tumorigenesis. Several cases known to the author developed their primary or metastatic lesions following the debilitating effects of a viral infection.

Tranquilizers are immunosuppressive and should be avoided in breast cancer patients. Stoll noted that their use *before* diagnosis was significantly greater in breast cancer patients who developed metastases or recurrence within a year.(806) He also noted that tranquilizer use increased two to three fold *after* diagnosis of breast cancer.(407)

Due to Advanced Age of Patient

In general there is declining immune reactivity with advancing age, therefore in determining the comparative efficacy of any form of therapy for breast cancer it is absolutely essential that the patients be age-matched.(209)

Mueller analyzed survival in 3,500 breast cancer patients in Ontario and found that the older women seem to be the high risk group. More than half the youngest women have survived longer than 20 years, with the same stage, the same operation and the same cell type as that in the older group, whose half survival time is approximately seven years.(593)

ENVIRONMENTAL FACTORS, INCLUDING NUTRITION AND TRACE ELEMENTS

Dietary components may have opposing effects on tumorigenesis, i.e., protective or predisposing, and the consequence to the host will depend upon the balance between these opposing forces.(8) The modifying effect of diet and nutrition may be exerted through specific effects on a) intestinal bacteria and substrates for bacterial metabolism, b) microsomal mixed-function oxidase system, c) endocrine system, d) immunological system, e) availability of metabolites for cell proliferation and f) rate of carcinogen transfer and duration of exposure to carcinogen. More research is needed to elucidate the interaction between diet and each of these factors.(8)

As regards breast cancer, diet may promote or inhibit tumorigenesis through its effects on hormonal and immune systems.(360) Nutritional factors are more likely to act as promoters rather than initiators of tumor growth.

A recent study in Northern Alberta revealed significantly increased risks of developing breast cancer with more frequent consumption of beef, pork, and sweet desserts, as well as elevated risks with use of butter at the table and for frying with butter.(513)

Goldin et al reported that in vegetarians a greater amount of biliary estrogens escape reabsorption and are excreted in the feces. The differences in estrogen metabolism may explain the lower incidence of breast cancer in vegetarian women.(322)

Armstrong et al noted that in comparison with matched nonvegetarian women, postmenopausal vegetarian women had lower urinary levels of estriol and total estrogens, lower plasma prolactin levels and higher plasma sex hormone binding globulin (SHBG) levels. These hormonal differences may explain the lower rates of endometrial and possibly breast cancer that have been observed in vegetarian women.(22a)

In countries such as England and the United States, where cancer incidence is high, the feces contain significantly more bacteroides and bifidobacteria, but fewer streptococci and lactobacilli than those from Ugandans, where cancer of the breast and colon is rare. Bacteroides are very active in degradation of bile salts which may produce carcinogens. Further study is needed on the bacterial flora of the bowel.

The incidence of breast cancer is comparatively low in India. Although it differs widely among various religious communities, the Hindus from Sind and the Parsis (Zorastrians) have a considerably higher incidence than other communities such as the Moslems.(657) This is believed to be due to differences in diet.

Diet During Early Years

The association of early menarche with higher risk, and early first pregnancy with lower risk, suggests that events during teenage years may be determinants of breast cancer.(360) If this is true, information on diet, nutritional status and hormonal patterns before and during teenage years may help to explain differences in subsequent risk.(360) Although the association between obesity and mammary cancer are not entirely consistent, it does seem clear that body fatness at menarche and during postmenopausal years may influence hormonal synthesis and metabolism. There is need for data relating dietary factors to hormone synthesis and metabolism.(360)

Diabetes: It is significant to note that incidence of diabetes mellitus is eight times as great in women with breast cancer than in women of comparable age in the general population.(697)

Dietary Fat

Wynder et al believe the key environmental element which is associated with breast cancer on the basis of a number of lines of evidence is *dietary fat*.(916) Thus the reduction of intake of fried foods and of fat, with carcinogenic and indirect promoting effects will lower the risk for cancer of the breast, also colon and prostate cancer. An additional benefit will be a lowering of the risk for coronary heart disease.(887)

The role of adipose tissue in breast carcinogenesis (either acting as a reservoir or depot for carcinogens) has been discussed for over 30 years. Since adipose tissue rapidly takes up and slowly releases lipid-soluble agents, it has been proposed that such tissue surrounding ductal cells in the breast may contribute to their susceptibility to cancer by prolonged exposure to lipid soluble carcinogens of exogenous or endogenous origin.

Direct changes in the lipid composition of cell membranes induced by diet could have far-reaching structural and functional effects on membrane permeability and the activity of membrane-bound enzyme systems.(696)

Indirect mechanisms by which dietary fat stimulates mammary tumor growth include altered function of a) immune rejection responses; b) mixed-function oxidases; c) endocrine control systems. This is discussed in detail by Reddy et al.(696, pp. 307–308)

They concluded that: 1. Dietary fat exerts its effects on the promotional phase of breast carcinogenesis. 2. Promoting agents, such as dietary fat, play a more significant role in

determining the outcome of the neoplastic process when the initiating carcinogen dose is low, than when it is high. 3. The total quantity of dietary fat, irrespective of qualitative factors, is a central factor in the high fat effect. 4. A certain threshold of essential fatty acids is a necessary requirement for full expression of the high fat effect. 5. The tumorigenic response to dietary fat consumption is saltatary or discontinuous, rather than linear or graduate, in nature.(696)

Enig et al believe that processed vegetable fats should be more carefully investigated as regards their relationship to cancer incidence.(243)

Internationally, lactase sufficiency and dairy product consumption after childhood are positively associated with breast cancer mortality.(310)

Hems reported that the influence of fat intake appears to be more important for breast cancers which develop in later life.(374)

Chan and Cohen's studies indicate that the effect of high fat intake on mammary carcinogenesis is mediated by prolactin.(132)

Miller et al reported on a case control study in four areas of Canada in which 400 cases of breast cancer matched by age and marital status were compared with neighborhood controls. The study produced evidence of an association between an increased uptake of nutrients, *especially total fat*, in both menopausal and premenopausal breast cancer patients. Its consistency with other evidence both experimental and international suggests it is causal.(569)

The incidence of breast cancer in Japanese women is only four per 100,000 as compared to 22 per 100,000 in white women in the United States.

Migrant studies indicate that environmental, rather than genetic, factors appear to be responsible for differences in breast cancer incidence found in Asian and Western women. Of the numerous environmental elements, nutritional differences are the major focus of attention. Since a high fat diet stimulates breast cancer development and circulating *prolactin* levels in animal models and is also typical of the diet of Western women, it may be reasonable to assume that high fat intake may exert its effect on breast cancer by way of the endocrine system.

Some investigators believe that fat soluble carcinogens localize in high concentrations in breast fat cells. *Thus the increased mass of breast fat in Caucasian women may act as a depot for the prolonged release and local diffusion of carcinogens into breast tissue.*

Gut bacteria can produce estrogens from the biliary steroids present in the colon. Since the amount of biliary steroids found in feces is correlated with the amount of fat in the diet this could explain the relation between the amount of dietary fat in the incidence of breast cancer.(386)

Japanese women seem to have not only less cancer of the breast, but less biologically active breast cancer when they do develop it.(131;608) As to possible reasons for this, the Japanese consume much less beef or meat fat than other women.

In Japanese women breast cancer is the disease of the middle aged, whereas in the United States it is the disease of the aged. The overall survival rate in the Cancer Institute Hospital in Tokyo is 63.8%, while at the Vanderbilt University Hospital in Nashville it is only 46.9%. Among American women the menopausal status is a critical factor for prognosis of breast cancer but it is not among Japanese women.(725)

In addition when Japanese migrate to Hawaii or the United States their incidence of breast cancer increases markedly.(632) This suggests that certain American foods are important as possible dietary factors related to the occurrence of breast cancer in women.(923) Migrating Japanese women have increased intakes of fats which may be responsible for this increased incidence.

Unfortunately, there has been a sharp increase in the incidence of breast cancer in Japan since 1966, in a period in which there has been a 250% increase in dietary fat intake.(742a)

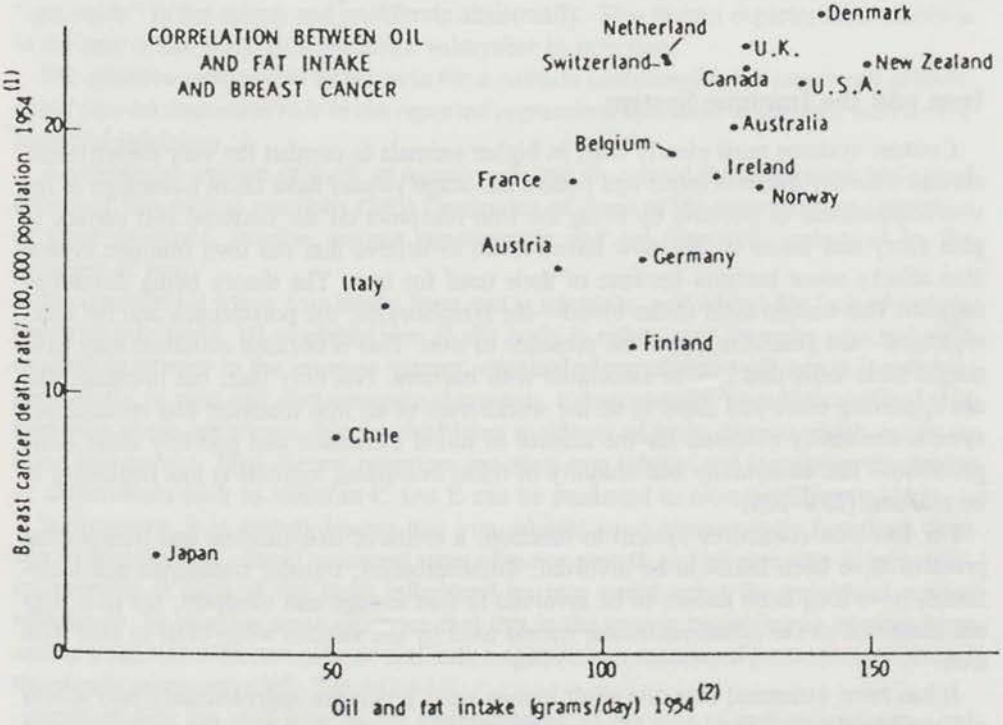
Dairy Products and Intestinal Lactase Deficiency

Internationally, breast cancer mortality is correlated with intestinal lactase deficiency and dairy product consumption from childhood. These findings suggest that women should avoid milk, butter, and cheese in their diet, especially if at high risk of breast cancer due to genetic or other factors.

Trace Elements

Iodine: Another factor which may protect Japanese women is the iodine content in the fish and kelp used in the diets of Japan, which is lacking in the Alpine areas of Europe and certain parts of the United States.

Geographic differences in the ratio of breast, endometrial and ovarian cancer appear to be inversely related with dietary iodine intake. Endocrinological considerations suggest that a low dietary iodine intake may produce a state of increased effective gonadotropin stimulation, which in turn may produce a hyperestrogenic state characterized by a high production of estrone and estradiol and a relatively low estriol to estrone plus estradiol



(1) Segi, 1964
(2) U.N. Food and Agricultural Organization, 1960

ratio. This altered endocrine state may increase the risk of breast, endometrial and ovarian cancer. Increasing iodine intake may reduce the risk of these cancers.(246–248)

Selenium: Female breast cancer incidence is lower in areas of the United States with adequate or high selenium supply than in areas which are low or deficient in this essential trace element. It is possible that human breast cancer incidence and mortality could be lowered by appropriate dietary selenium supplementation.(739)

Studies at Roswell Park Memorial Institute indicated enhancement of mammary tumorigenesis occurred with dietary *selenium deficiency* in female rats on a high polyunsaturated intake. These findings suggest the need to evaluate the potential use of selenium supplements in the prevention of breast cancer in the human population due to selenium deficiency, especially in countries with a high fat consumption.(421)

Iron: Iron is one of the most common single elements, making up one third of the earth. Its involvement in the early history of life is fascinating because the earliest living forms, the bacteria, have developed extremely efficient ways to utilize it and clever biological systems to reduce it or solubilize it. In many cases the capacity of bacteria, such as those causing tuberculosis to multiply seems to be dependent on their being in an environment with plentiful iron. The fact is that many deadly bacteria need iron to be infectious. Some bacteria apparently have the capacity to break down our red cells during the process of infection. In this way they release iron from the red cells and use it themselves. Bacterial systems like these which are iron-dependent have been very carefully studied and beautifully analyzed in the field of microbiology.

Iron and the Immune System

Counter systems must clearly exist in higher animals to combat the very clever mechanisms whereby bacteria infect and poison us. Some viruses have taken advantage of the iron requirement of bacteria by using the iron receptors on the bacterial cell surface to gain entry and infect it. We now have reason to believe that our own immune system also attacks some bacteria because of their need for iron. The theory being developed suggests that certain cells of the blood—the lymphocytes, the polymorphs and the macrophages—are geared to detect the presence of iron. This is because evolution may have taught these cells that iron is associated with bacteria. Not only that, but immune cells are appearing more and more to be the workhorses of an iron transport and reutilization system absolutely essential for the control of blood formation and possibly other basic processes. The complexity and ubiquity of these iron-based systems is just beginning to be realized.(203–205)

For this iron commerce system to function, a series of iron-binding and transporting proteins have been found to be involved. These proteins, ferritin, transferrin and lactoferrin, have long been known to be involved in iron storage and transport, but now they are identified as the actual molecular means used by the various white cells to deal with iron.

It has been estimated that one adult human male processes approximately two billion old red blood cells every day. This represents 38 mg. of iron which has to be recycled by the immune system. Ninety percent of this goes to new red cell production, the other 10% remain in storage in the macrophages of the immune system and the liver, ready for reutilization as needed.

Before the development of antisepsis, vaccines and antibiotics we were exposed to all types of bacterial infections and infectious diseases, and we were not given iron supplements. At present, infections occur rarely and when they do, they are rapidly controlled by antibiotics. Iron supplementation of bread, milk and in multi-vitamin preparations ensures that the majority of the population, in countries like the U.S.A. and Sweden, is taking not only adequate amounts of iron, but in some cases (men and postmenopausal women) too much.

Our bodies' mechanisms for dealing with excess iron may break down or get overloaded. Control of iron levels is normally exercised at the point of entry in the small intestine. Normal people stop absorbing iron the moment they have sufficient iron in circulation and in storage. But a person with an abnormality of this controlling mechanism will be at risk if exposed to too much iron, i.e., in drinking water, eating too much meat, or taking too many iron supplements.

Iron and Cancer

Recent studies of the nutrient requirements of cancer cells *in vitro* and *in vivo* have shown that cancer cells utilize iron in a fashion possibly similar to that of bacteria. It is suspected that the requirement of iron by cancer cells is related to its utilization for DNA synthesis. Since iron is processed by the lymphoid system, particularly by the spleen where old red blood cells are broken down to have their iron reutilized, this is the system which gets overloaded first. A number of things happen as a result, the most obvious being that lymphocytes, which have been trained by evolution to go to iron rich sites, "get stuck" in the spleen and proliferate abnormally. This in turn depletes their numbers in the rest of the body so it becomes vulnerable to infection.

The effective competition of bacteria for a nutrient indispensible for tumor cell growth, could play an important role in the reported regressions of cancer associated with severe bacterial infections.

A substantial amount of work in recent years has elucidated the deleterious biological effects of free radical reactions.(363) Generation of some of the most toxic end products of these reactions, involve oxygen consumption and are drastically enhanced by the presence of iron.

In communities where iron intake from diet is adequate, and where, for lack of serious bacterial infections, all available iron in the body is either used to make new red cells or stays in storage in the immune system, eventual accumulation with age is inevitable, particularly in men and postmenopausal women. It has recently been hypothesized that high iron stores are responsible for the higher incidence of heart disease which occurs in these two groups. Thus dietary regimens reducing iron intakes and increasing the intake of antioxidants such as vitamins C and E can be predicted to increase lifespan.(363)

In summary, it is already known that iron inhibits some immunologic functions. Iron can be envisaged as critical to several steps of tumor growth and progression. In principle, intervention at each of the steps influenced by iron could arrest the growth of cancer effectively. In practice some evidence that this is the case is beginning to emerge from cancer treatment with monoclonal antibodies against iron-associated proteins (ferritin and transferrin receptors).(202–204;642;844)

Such studies are vital now to our understanding of the role of iron in immunity and cancer and the pioneer work of de Sousa at Sloan-Kettering Institute in New York is fundamental. It will have wide ramifications, scientific and clinical, in the understanding and treatment not only of cancer but of other diseases such as rheumatoid arthritis and

heart disease. It will also have important consequences for nutrition and help our understanding of bacterial infections and the way we combat them.

Alcohol and Drugs

The U.S.A.'s Third National Cancer Survey revealed that alcohol ingestion was associated with a higher occurrence of cancers of the breast, thyroid and malignant melanoma. Data from other studies support the first two associations. Alcohol stimulates anterior pituitary secretion of prolactin, thyroid stimulating hormone. Under such stimulation these three target tissues exhibit increased susceptibility to the development of malignancy. In addition to alcohol, several common drugs acting in a similar manner could be cancer promoters, including reserpine, methyldopa, phenothiazines, d-amphetamine, tricyclic antidepressants and antihistamines. Over 20,000 of all new breast cancer cases each year in the U.S.A. could be preventable if this hypothesis is correct.(904)

Overnutrition

De Waard and his colleagues were the first to suggest an association between *overnutrition or obesity* and breast cancer.(208) A study was made in the cities of Rotterdam and the Hague, in the Netherlands, and in Aichi prefecture in Japan, to assess the effect of weight and height (and their combinations) on the age-specific incidence of breast cancer. It is based on a comparison between 1,006 cases of breast cancer and 4,201 women from the general population. The results suggest that about half the differences in incidence between Holland and Japan can be attributed to differences in body weight and height. In breast cancer patients in Rotterdam and the Hague those with axillary metastases were significantly heavier, but not taller than those without nodal involvement. A hormonal factor related to body weight might be responsible for the increased incidence and more rapid course of breast cancer in women with a large body mass.(211)

Donegan et al discussed this in 1978 and concluded that diet and weight reduction may represent empirical means for improving the prognosis of heavy individuals with early stages of breast cancer.(223) They found an increased incidence of adrenal related diseases, such as obesity, diabetes and hypertension in postmenopausal women with breast cancer and postulated that the disease in older women is related to adrenal estrogens, whereas in younger women it is ovary related. Their hypothesis is based on these findings: a) after the menopause adipose tissues instead of the ovaries or adrenals produce estrogens; and b) estrogenic cervical smears persist postmenopausally in overweight women.(210)

In Taiwan women weighing more than 55 kg. had a breast cancer risk twice that of those wieghing less than 45 kg.; the risk was stronger and more regular among women over 50 than among younger women.(502)

N. F. Boyd in Toronto found that in women with breast cancer weighing less than 140 pounds, the survival rate was roughly 60% 10 years following surgery, and there was no difference between those having adjuvant therapy and those that did not. Of the patients weighing more than 140 pounds who had no adjuvant therapy the overall survival was only 18%. Thus body weight is an important variable that oncologists should consider in hormone-related studies of breast cancer. Weight reduction might improve survival.(94)

Choi et al found a strong associated with increased weight both at the time of menopause and the year preceding diagnosis of breast cancer in their study of four areas in Canada.(137)

In women, dietary modification and lifestyle affect the risk of breast cancer and may alter the hormonal status.(387) Hill et al noted that in experimental animals diet can alter the incidence of induced mammary tumors. In their study a high fat diet increased the incidence of dimethylbenzanthracene-induced tumors in rats. This increased incidence was lowered and the effect of a high fat diet obliterated by an anti-prolactin drug, bromo-ergo-cryptine (C.B. 154, Sandoz, Switzerland). When healthy nurses were changed from the Western diet to a vegetable diet their menstrual cycle was shortened by two days and their prolactin and testosterone levels decreased. Hill et al concluded from their studies that dietary factors influence tumor incidence and hormone profile in rat mammary cancer and also the hormonal status of women.(387)

Hems compared annual per capita intake of calories, carbohydrates, sugar, fat and meat in 22 countries with mean mortality rates from breast cancer. He found a positive correlation between sugar and fat intakes and mortality rates.(374)

Stocks, in England and Wales, found positive associations between milk, butter and cheese intakes and breast cancer mortality and negative associations between other fats such as margerine and mortality.(801)

About half of the Seventh-Day Adventists follow a lacto-ovo-vegetarian diet, and almost all do not eat pork nor drink alcoholic or caffeine type beverages. Breast cancer mortality in this group is one half to two thirds that of the general U.S. population. Phillips collected food frequency data in a prospective study of 100,000 Adventists living in California. After four years there were 77 cases. These were each matched by age and race to three controls from the study population. Comparisons of dietary data showed that the frequency of eating five food items were associated with breast cancer: fried potatoes, hard fat (butter, margarine or shortening) for frying, all fried foods, dairy products except milk, and white bread.(669)

A mechanism whereby fat may increase breast cancer risk in humans has been suggested by Hill et al. They found that persons on high fat diets have higher proportions of active anaerobic bacteria in their intestinal flora and secrete more biliary steroids than those on low fat intakes.(386) *These bacteria are able to synthesize estrogens, such as estradiol and estrone from these steroids which are potentially carcinogenic to the breast.*

There is a need for more data relating dietary factors to the synthesis and metabolism of estrogens. As noted above, it is possible that the production of estrone in fat tissues is greater in obese postmenopausal women than those of normal weight. In younger women, the synthesis of estrogens by the ovaries may depend upon a critical level of body fatness.(360)

More collaborative studies should be planned by epidemiologists, nutritionists, endocrinologists and oncologists to provide data concerning the interrelationships of diet, nutritional status, hormonal systems and breast cancer. Their findings might help us develop preventive health programs.(360)

Constipation and Breast Cancer

During the first two decades of this century, several distinguished surgeons noted that lumpy breasts, chronic cystic disease and possible breast cancer were frequently found in women with severe constipation or "chronic intestinal stasis" as it was then called. They reported that the cystic condition resolved after dietary or surgical correction of the constipation and autointoxication.

Papatestas et al's recent findings support these earlier clinical observations.(650) They showed that the non-lactating breast takes up and secretes chemical substances from the

blood into breast fluid. It is therefore likely that many chemical substances originating in the colon may enter the blood stream and reach the breast. They suggest that potentially toxic substances may have damaging or even carcinogenic effects upon breast epithelium.

In additon to carcinogens and mutagens, intestinal bacteria have been shown to synthesize estrone, estradiol and 17 methoxyestradiol from feces. Glucuronides of estrogen also gain access to the intestinal tract by hepatic excretion into bile. In the colon and estrogen-glucuronide linkage may be attacked by B-glucuronidase produced by bacteria and epithelium especially in individuals on high protein-high fat diets. This released estrogen may then be absorbed from the colon and may have additional stimulatory effects upon the breast. Women on vegetarian diets tend to excrete the estrogen-glucuronide in the feces, whereas carnivorous women have an intestinal flora capable of splitting the estrogen-glucuronide linkage.(650) Oncologists dealing with breast diseases should now give greater consideration to the importance of diet and the prevention of constipation by better nutritional regimes.

DELAY IN DIAGNOSIS AND THERAPY

Whenever the management of breast cancer is under discussion, the importance of early diagnosis and prompt treatment is stressed. Traditionally it has been considered that not even a single day should be lost in instituting treatment for breast cancer,(352) and the general teaching has been that the greater the delay, the worse the prognosis.(76) However, recent studies indicate that the time-oriented conventional view concerning the growth and dissemination of breast cancer may represent a misleading oversimplification.(279)

Bloom made a plea for efforts to reduce loss of time in seeking treatment in order to save or prolong useful life for the individual patient, a factor often overlooked in mass statistics. However, he noted in analyzing the available data in 1965 that most authors are unable to demonstrate an appreciable deterioration in prognosis in breast cancer with increasing duration of symptoms. In this series of 1,200 cases at the Royal Marsden Hospital in London, treated chiefly by radical surgery with or without ancillary irradiation, delay in treatment did not appear to influence prognosis adversely judging by the 5 to 20 year survival rates.(76) This was due to the fact that the more rapidly growing and more lethal grade III tumors tend especially to be found in patients who seek early treatment. On the other hand, the essentially less malignant grade I lesions are found more often in patients with a long history. Thus, the distribution of tumor grades tends to counterbalance the influence of delay in survival rate.

With increasing delay for each grade of tumor, the incidence of Stage I decreases while that of Stage III cases increases. Since half the breast cancer patients do not seek advice in large cancer hospitals until their tumors are over 5 cm. in diameter or ulcerated, it has been difficult or impossible to improve end results with conventional methods of treatment. With extensive disease, host resistance is apt to deteriorate.

Women whose initial symptoms do not include a lump are slower in consulting their physician and he is more likely to delay in referring them to a specialist. Although it is true that for about 78% of patients a lump *is* the initial symptom, there should be more emphasis in health education on the necessity to consult a doctor for any abnormal breast symptom. These include dimpling, inverted nipple, and nipple discharge. Such advice must be done in such a way that it does not provoke anxiety.(530)

Fisher et al analyzed the influence of duration of symptoms to treatment failure in 1,539 patients with clinical Stage I and II invasive breast cancer. They found although the proportion of patients with positive axillary nodes was suggestively related to duration of symptoms, *that there was a trend toward reduction in treatment failure rate in patients whose symptom period was not too brief.*(279) They suggested that this finding possibly reflects the importance of host-tumor relationships in the natural history of patients with breast cancer. Surgical ablation of these tumors too soon after onset does not provide sufficient time for the patient to mount an immunological reaction against the tumor.

Other data support this finding. In a study of factors affecting prognosis in recticulum cell sarcoma of bone treated by Coley's mixed bacterial vaccine, it was found that a larger number of successes occurred in patients in whom treatment was begun 6 to 9 months after onset.(571) Ferguson in 1940 also noted a better survival in patients with osteogenic sarcoma who were treated later rather than earlier.(605; ref. #64) Three breast cancer studies confirm the fact that there is an improved survival rate and fewer recurrences in breast cancer patients with biopsy and delayed mastectomy compared with immediate mastectomy.

Huguley and Brown reported that in a study of 2,092 women with breast cancer, those who had practiced breast self-examination (BSE) had earlier cancer than those who had not. This was true of both black and white women all educational and economic levels and each age group. The practice of BSE increased as the educational level rose and diminished as age advanced.(411)

DIAGNOSTIC PROCEDURES

Mammography for Precancerous Lesions or Risk Factors

Brisson et al conducted a case-control study at two Boston, Massachusetts hospitals to evaluate the relation of anatomic features of the breast visible on the xeromammogram, to the risk of breast cancer.(97) The cases were 408 women with newly diagnosed breast cancer and the controls were 1,021 women without signs or symptoms of breast disease. The features of the breast were assessed were the "parenchymal pattern" as defined by Wolfe(911) and specific radiologic characteristics which are components of the parenchymal pattern classification. Women whose mammogram showed the P2 or DY parenchymal patterns were at elevated risk compared to the N1 pattern. These findings were observed only among women 20–59 years of age. In this group women with nodular densities in 60% or more of the breast appeared to have a five-fold increase in risk compared to women without nodular densities.(97)

Mammography to Detect Breast Cancer

As regards mammography as a means of providing earlier diagnoses, a controlled breast cancer screening program (annual physical examination plus mammography conducted by Health Insurance Plan of New York) showed no benefits whatsoever for women under 50, but there was a benefit for those over 50. The possible dangers of inducing breast cancer from repeated mammographies over many years must also be considered. The HIP study may be outdated in that it was done in the 1960's and mammographic techniques have improved considerably in the last decade.

Continued progress in mammographic techniques, with marked reduction in radiation exposure, now makes mammography an essential part of the workup of any breast problem in women over the age of 50.(98a,460a) Breast patterns alone cannot be used as the basis for determining high or low risk patients, but they can guide the clinician in deciding what are the proper intervals between mammograms. With increasing use of mammography, emphasis has now changed from the diagnosis of obvious cancers to the evaluation of minimal or questionable mammographic findings. Such occult masses of calcifications require needle localization with or without specimen radiographs to insure removal of proper areas for histologic study.(772) These techniques should help prevent delay in diagnosis. A recent study indicates that the radiographic appearance of breast parenchyma provides a method of predicting who will develop breast cancer.(911)

Thermography

Some oncologists believe that thermography may make a significant contribution to the evaluation of patients suspected of having breast cancer, not only as a predictor of risk, but also to assess the more rapidly growing neoplasms.(312)

Needle Biopsy

Fine needle biopsy with cytologic analysis has become more popular as a detection method, and core needle biopsies with histology are sometimes used. Analysis of nipple secretions for chemical markers or for cytologic diagnosis may become more reliable. However, the judgment of an informed and skilled examiner still remains the best method for the detection of early breast cancer.(736)

Overuse of Diagnostic Procedures

In recent years oncologists dealing with breast cancer patients have multiplied the number of diagnostic tests to which these women are subjected. Some are vital, some may be superfluous or repeated too often. For example, the incidence of positive bone scans performed at the time of mastectomy may range as low as 1.9%.(62) Although a positive scan is a bad prognostic finding, it identifies only a few of these patients who subsequently develop a major recurrence and lymph node biopsy at mastectomy gives a great deal more information in this respect.

The Nottingham Study of 354 women showed an incidence of positive bone scans of 2.3% at time of mastectomy. However, *only one case (0.3%) was positive without other x-ray evidence of metastases at the same site*. This represents an enormous effort for a very tiny yield of information. In addition, it was found that there are nearly as many false positives as true positive scans. This group noted that scanning at one and two years after mastectomy still yielded a very small bit of useful information for a great deal of effort. Each scan costs from $262–$330 in the United States (£30 in the United Kingdom). The cost for this one study in Nottingham was £23,190. Since at least 100,000 bone scans are done in the United States each year, the cost is over $30,000,000. Despite these facts, routine bone scanning is increasingly being used all over the United States and the United Kingdom, but this procedure is difficult to justify.(62) However, a single base line bone scan for future reference is important in the overall management of breast and prostate cancers.

Another important factor to consider is that scanning can add significant psychologic stress, which is immunosuppressive.(94b) Greater clinical judgement in ordering too many scans for elderly patients is essential.

Brewin believes that the conversion of a guarded prognosis to a gloomy one is far more likely to harm the quality of life than to help it.(94b) He noted that the best—some would say the only reason—for ordering a test is to modify management if the findings so indicate. He added that overinvestigation can lead to overtreatment with its attendant risks. Some patients have a low threshold of comfort, anxiety or both. Others previously stoical, may change as they grow older or in the course of a long illness, so that even a simple injection is dreaded, to say nothing of a long wait in a hospital corridor or lying on a rock-hard x-ray table, wondering what is going to happen next.

Interactions

CONCURRENT BACTERIAL INFECTIONS AND FEVER

For over 200 years physicians have observed dramatic "spontaneous" regressions of various types of neoplastic disease during or following acute concurrent infections.(602–619) A large number of authors recorded their observations of the beneficial effects of such infections, as well as those in which inflammation, fever or incomplete surgery were involved. Our infection monograph contains 1,032 references. We have also assembled many more such cases that were seen all over Europe and the United States but had not been published.

Vautier (1813) discussed the question of whether cancer may be cured by the sole forces of nature. He had found "several cases in searching the writing of the most careful observers in which cancer terminated happily by the development of gangrene."(858) We have abstracted 22 such cases in which "gangrene" developed spontaneously or by inoculation, of which the majority were breast cancers.(611) Recent research on the Tumor Necrosis Factor suggests that in these patients a combination of bacteria had induced the tumor necrosis factor which these early physicians had designated as gangrene.(611)

Such cases inspired physicians in the 18th and 19th century to induce "laudable pus, setons or issues" in their inoperable cancer patients as the first form of immunotherapy.(816)

Bayle and Cayol (1812) reported that gangrene could become a means of cure in cancer of the breast.(45a) They had seen the entire tumor slough off by the action of gangrene. The wound resulting from this separation heals in a short time. They cited Garneri's remarkable case.

Tanchou, a well-known physician in Paris, collected 300 cases in the literature prior to 1844, of breast cancer treated medically. (No anesthesia was available in that period.) He discussed the role of gangrene as follows: "It is remarkable that after hemlock (conium) it is gangrene that caused the largest number of cures. Gangrene may be considered a therapeutic agent, whether it occurs spontaneously or is induced medically." Rigal de Gaillac, Sr. induced gangrene in a small incision or by applying gauze dressings soaked in gangrenous discharges on open cancers. One knows that Dussossoy had the idea of inoculating "hospital gangrene" in cancer patients having thus cured an ulcerated carcinoma. The success of this audacious experiment was complete, the ulceration destroyed the entire tumor which sloughed off on the 19th day. Dussossoy then concentrated on controlling the progress of the gangrene, succeeded in doing so, and in a few days, the ulcer became bright red and covered with healthy granulations. Tanchou added: "Here gangrene seems to have replaced live cautery, caustics or the scalpel."(816)

Until our study began over 40 years ago no one had attempted a) to determine which types of tumors were most frequently benefited from bacterial infections; b) which types of infections or bacterial products were most apt to be effective; c) whether other infections (viral or protozoal) might also be beneficial or might actually have a deleterious effect.

The beneficial effect of bacterial infections in *breast cancer patients* is apparent from the considerable number of reported cases (see Part II, Series A–F). The majority of complete regressions occurred following erysipelas, the next most effective infections

being suppuration or abscess (mostly staphylococcal). Only six cases of inoperable breast carcinoma with concurrent nonpyogenic infections were found. These included three cases of tuberculosis and one each of malaria, syphilis, typhoid. Four of these patients had complete regressions. In this connection it is of interest to note that Wolff reported no case of cancer had been found in patients who had had typhoid.(912)

It is clearly evident that concurrent viral infections may *lower* the resistance of cancer patients and may play a role in the development of the primary, the more rapid progress of the disease or its reactivation.(611;617)

In the 15 operable cases in which pyogenic infection developed before or after surgery, 10 had suppurating wound infections (staphylococcus). Only two of these 15 patients died of cancer, one 5 years and one 20 years after onset; 11 were traced well 5–40 years; 3 were traced less than 5 years. (Series E)

As regards the beneficial effects of gangrene, Garneri, the chief surgeon of a hospital in Turin, Italy, published his interesting case (1810, 1811) in which an inoperable, extensive carcinoma of the left breast was "destroyed completely by inflammation and gangrene," following a febrile episode.(308) This observation led him to conclude that one should search for a substance capable by its application of gently destroying the life of cancer tissue. He added: "When such necrosis had been produced in these lesions, one should not attempt to limit it, but on the contrary to encourage it until it had destroyed the entire neoplasm." (See Part II, Series A, Case 7 for this case.)

Walsh, in England, in the same period, was also aware of the beneficial effects of gangrene, and stated: "The inoculation of the matter of common and hospital gangrene has been practiced, with the design of imitating the natural processes of cure."(868, p.165)

Mohr (1888) reported a remarkable case (see below, Part II, Series A, Case 19) in which an extensive, inoperable, ulcerated breast carcinoma with axillary, supraclavicular and skin metastases and advanced cachexia, had developed in an 87 year old woman. She developed erysipelas. All evidence of disease disappeared, and the general condition improved marvelously. She then fractured her left humerus in a fall. Repair was rapid and in 24 days it was possible to begin motion of the shoulder and elbow joints. In reporting this case, Mohr emphasized the rapid disappearance of all signs of the malignant growths and cachexia and *also the rapid repair of the fracture occurring so late in life, and so soon after the regression of the neoplasm as a result of erysipelas*. He added: "In the light of this case, would one be justified in inoculating a patient suffering from cancer . . . with . . . erysipelas, to bring about a possible obliteration of the neoplasm?"(578) Mohr was the first physician outside Europe to suggest this. W.B. Coley actually did so three years later, in 1891.(148)

The beneficial effects of fever in an advanced recurrent case of bilateral ductal breast cancer with widespread metastasis including pleura was noted in September 1979. At the time the febrile reactions occurred, due to a single intrapleural infusion of 1×10^7 BCG (Tice) and a transfusion of red blood cells, prognosis was regarded as about two months. Fever persisted for 1 month with diurnal fluctuations from 100–103.5° F and one spike to 105.8° F subsequent to red blood cell transfusion. The severe dyspnea due to pleural effusion ceased and the general health improved markedly, so that the patient was able to go skiing and ride horseback, including jumping. Her only other treatment that autumn through June 1981 consisted of i.d. injections of 0.1 ml of *Salmonella typhi* vaccine every eight weeks and 10 mg human erythrocyte-derived Thomsen-Friedenreich antigen. This remarkable remission lasted approximately seven months. Death occurred August 20, 1980, 6¼ years after onset.(122)

Lent C. Johnson, pathologist at the Armed Forces Institute of Pathology, in a personal communication wrote, July 21, 1966: "I have vivid memories of occasional cases of breast cancer at Cook County Hospital (Chicago) that seemed to be arrested or cured when the patient developed erysipelas. Of course, at that time, I did not have the background for critical assessment, but physicians of that day whom I respected, pointed out such cases. Some years later, I had an opportunity to see cases of neuroblastoma with spontaneous cure, (including cases with metastases . . .) I was impressed with the fact that some of the children had very severe, almost lethal infections shortly after the diagnosis was made, following which their disease seemed to arrest."

Inflammatory Exudates

The known cases illustrating the dramatic beneficial effects of inflammatory exudates are given in Part II, Series C. MacKay's(532) and Tuffier's(847) cases are given in detail since they are of special interest (see Cases 2 and 3 following the table.)

Induced Infections

Fehleisen isolated the streptococcus in 1882. He was the first physician to inoculate living cultures of streptococci in an attempt to induce erysipelas in cancer patients.(254) Others in Europe quickly followed, and in 1891 W.B. Coley was the first to do so in the United States. (See Part II, Series E, for 11 inoperable breast cancer patients so treated. Fehleisen's first case is given in detail.) Matagne, of Brussels, Belgium was the first to inoculate living cultures of streptococci in an *operable* breast cancer. (This history is included as Case 16 in Part II, Series D.)

As mentioned above, the first reported cases in which suppuration ("laudable pus") was actually induced therapeutically in cancer patients were cited by Tanchou in 1844.(816) Five breast cancer cases so treated are given in Part II, Series F. These physicians applied septic dressings, setons or cauteries or syphilitic pus. In one case inoculation of malarial blood was given. The latter caused no effect, while complete regression occurred in the other four cases.

The data assembled here clearly indicate the powerful therapeutic effects which various types of bacterial infections may exert in breast cancer. However, modern oncologists tend to see only the life-threatening bacterial infections which develop in terminal cancer or leukemia patients following immunosuppressive conventional modalities; hence they are not clearly aware of the beneficial effects such infections may have if they develop prior to the terminal stage or before such therapy is given. The indiscriminate use of antibiotics should be avoided in cancer patients, instead one should administer injections of mixed bacterial vaccines to stimulate and reinforce the immune defenses. This procedure is being used in certain burn units to prevent infections in these severely compromised patients, and in treating cancer and leukemia at the present time.

HEAT AND INFLAMMATION

The beneficial effects of heat and fever play a role in cancer incidence and response to therapy.(614) In Japan the daily use of the *hot full bath*, (42°–48°C) may destroy

incipient cancers before they are clinically apparent. This practice may be one reason why the incidence of cancers of the breast, prostate, testis, ovary, penis and skin is very much lower in Japan than elsewhere. (Breast cancer incidence in Japan is only one-sixth that of the women in the United States.)(608) The few Japanese women who do develop breast cancer appear to respond to treatment with higher survival rates and histologically the immune reaction to their tumor is more active.(537) In this connection MacMahon et al found that intraductal, medullary and colloid tumors were relatively more frequent in Tokyo, and that tumors with circumscribed margins and a high degree of cellular reaction were also more frequently seen there than in a similar representative series seen in Boston, Massachusetts (U.S.) where more invasive histological types occurred more frequently.(537)

In Finland, where hot *sauna* bathing is a common practice, the incidence of breast and many other cancers is lower than in neighboring countries where the sauna is not used so frequently or intensively. The end results in Finland following lumpectomy and relatively low doses of radiation for breast cancer are better than in other countries using more radical surgery and radiation.(599;600)

Since we now know that heat and fever potentiate the response of tumors to radiation, and stimulate the immune defenses, such results are not surprising. Many surgeons and radiologists are now using various forms of hyperthermia alone or as an adjuvant to surgery and radiation with encouraging results. Accessible tumors such as breast cancer are particularly amenable to such treatment. (557;608;613) (See below for discussion of Hyperthermia, p. 87.)

In this connection it is of interest to cite the unusual report of Eason in 1776, which is given in detail in Part II, Series H: an extensive inoperable breast carcinoma regressed completely after the patient was struck by lightning!

"SPONTANEOUS" REGRESSIONS

Everson and Cole made a most comprehensive study of such cases in 1966.(252) In the past 40 years we have reviewed all available cases in which such regressions occurred following bacterial infections or fever.(611) The breast cancer cases in which such regressions occurred following infections appear in the present study in Part II. Because physicians or their patients did not always recognize that fever and infection can produce salutary effects on cancer, they did not always record such concurrent episodes, and some "spontaneous" regressions were reported in the literature without any known reason for their occurrence other than reduction of tumor burden by incomplete surgery or thoracentesis.(252)

Lewison cites Osler's report in 1902 in which he stated that such cases "are among the most remarkable which we witness in the practice of medicine, and illustrate the uncertainty of prognosis, and the truth of the statement that no condition, however desperate, is quite hopeless."(496)

It is our belief that "spontaneous" regressions are produced by some physical or psychic factor which increases our host resistance sufficiently to throw the balance in favor of the patient. We must learn to do this in the overall treatment of cancer patients by minimizing or removing the factors which depress our immune defenses and adding those modalities which can stimulate or protect them.

CELLULAR IMMUNE RESPONSES TO BREAST CANCER

Cellular immune competence and cell-mediated immunity to tumor antigens have been studied in breast cancer patients. Some of the tests for cellular immunity have revealed correlations with clinical course, and therefore, may be useful in the management of patients with breast cancer. Further studies of the relationship between immune reactivity and clinical course may also provide insight into important biological factors in regard to host defense against progressive growth of breast cancer.(372)

There is a lack of correlation between IgA concentration, lymphocyte count and recurrence in nonirradiated patients and a strong correlation in those given irradiation. This suggests that the pretherapy immune status may determine whether irradiation will benefit or harm a specific patient with metastases to axillary lymph nodes.(565) It suggests also that conflicting results in studies of immune factors in breast cancer may be the result of comparing irradiated and nonirradiated women.

They concluded that postmastectomy radiation is detrimental to patients with a low IgA concentration (200 mg/100 ml) and may improve survival in women with a high preoperative IgA level.(565)

Breast Cancer Therapy Analyzed in the Light of Host Resistance

RADICAL VS. CONSERVATIVE SURGERY

Disagreement about local-regional management of primary breast cancer is related to differences in perception of the biology of the disease. Other factors are secondary, and obscure the reality that all treatment must be related to biological considerations. Otherwise the basis for therapy is relegated to speculation and to personal experience.(272) Extensive laboratory and clinical studies in the United States, Canada and Europe have led to an altered concept of cancer biology. The National Surgical Adjuvant Project for Breast Cancer has made a major contribution to the change through findings from a series of prospective randomized clinical trials.(272)

In the 18th and 19th centuries there originated the assumption that cancer is a local disease which is curable if found sufficiently early. Those considerations set the stage for formulation of the principles that have completely dominated cancer surgery from the last decade of the 19th century until very recently. The rationale for the type of radical surgery that has been advocated during that period has been based upon the contention that a) a growing tumor remains localized at its site of origin; spreads to the regional lymph nodes (RLNs) and then systemically in an orderly defined manner; b) tumor cells traverse lymphatics by direct extension; c) RLNs provide an effective barrier to the passage of tumor cells; d) the bloodstream is of little significance as a route of metastasis; and e) a tumor is autonomous of its host.(272)

As a consequence of those considerations, there arose an hypothesis for cancer surgery that was totally anatomical in principle. The "proper" cancer operation consisted of removal of the primary tumor together with regional lymphatics and lymph nodes by en bloc dissection. Local-regional recurrences were considered to be the result of inadequate application of surgical skill rather than a manifestation of systemic disease. Radical cancer surgery based on these anatomical considerations persisted relatively unchallenged for 75 years.(272)

Stehlin et al suggest that the effort and brain power devoted to arguing the merits of various therapeutic procedures for primary breast cancer should be directed toward *learning the biological basis and control of metastases*. "If this were done both the science of oncology and the patient with carcinoma of the breast would benefit. Above all the patient should be treated as a human being, not as a vehicle for a cancerous breast."(784)

During the past two decades, as a consequence of a multitude of laboratory and clinical investigations in this country and in England, there has evolved an alternative hypothesis, which in its most simplistic terms considers breast cancer to be a biologically heterogeneous systemic disease involving a complexity of host-tumor relationships, and variations in local-regional therapy are unlikely to affect survival substantially.

Back in 1953 Gatch was one of the first to question the dogma that breast cancer rarely or never disseminates by way of blood vessels. He cited the work of Batson who demonstrated a primitive capacious system of veins without valves which extends along the

spine from the skull to the coccyx and which has numerous anastamoses with veins in the structures adjacent to the spine. He could fill this system with a radiopaque solution through a superficial vein of the breast. Thus cancer cells can reach the spine, ribs, brain and pleura by way of these spinal veins without passing through the lung. *He showed that coughing, straining and strenuous bodily movements may propel particulate matter along these spinal veins thus explaining the presence of metastatic breast cancer in the eye, brain and the proximal femur and humerus.*(311)

Breast cancer kills, not by its local, but by its metastatic growth. A crucial but unanswered question is what various surgical procedures, if any, do to prevent metastases? Tissue resistance to neoplastic growth is usually very powerful and Gatch believed that host resistance explains the anomalous and unpredictable behaviour of breast cancer. He also believed that we are deeply indebted to it for whatever good results we obtain from operations for this disease, and that these operations, if improperly done or unduly extensive and prolonged, may decrease or destroy this resistance.(311)

Beginning in 1955 Bernard Fisher undertook extensive laboratory and clinical investigations on breast cancer which have resulted in altering the therapy of primary breast cancer. These studies led him to conclude that a) regional lymph nodes do not trap disseminated tumor cells, b) there is no orderly pattern of tumor cell dissemination based upon temporal or mechanical considerations, c) patterns of tumor spread are not solely indicated by anatomical considerations, but are influenced by intrinsic factors in tumor cells as well as in the organs to which they gain access, and d) *regional lymph nodes are capable of destroying tumor cells*. Negative nodes are the result of the latter and/or because tumor cells traverse nodes rather than that a tumor has been removed prior to dissemination of its cells. The positive lymph node reflects a tumor-host relationship which permits the development of metastases rather than its being an instigator of distant disease. These studies also indicate that it is likely that breast cancer is a systemic disease from its inception.(261)

Devitt's views on breast cancer agreed with those of Gatch. As early as 1965 he stated that breast cancer patients do not do poorly *because* they have lymph node metastases *but rather because their host resistance is weak*.(206;207)

Recent studies indicate that in patients with tumors over 4 cm in diameter, and without evidence of lymphatic metastases, palpable enlargement of the axillary nodes is associated with a better prognosis. *It is logical therefore that unaffected nodes should not be removed or irradiated* because this increases morbidity without benefit to the patient, and may do harm by interfering with a natural protective response.(231)

The idea was, and still is held by many, that lymph borne tumor cells have one destination, lymph nodes; that tumor cells in the blood vascular system lodge in the first capillary bed they encounter; and that there is an orderly pattern of tumor cell dissemination based upon temporal and mechanical considerations. Fisher's studies in the last 15 years refute such a consideration. They revealed that whether tumor cells are initially disseminated via the blood stream or via lymphatics, the two vascular systems are so interrelated that *it is impractical to consider them as independent routes of neoplastic dissemination*. There is no orderly pattern of tumor cell dissemination.(259–278)

As noted above, Fisher revealed for the first time that regional lymph nodes (RLN) are not an effective barrier to tumor cell dissemination. Lymph nodes trap red blood cells but tumor cells not only pass through nodes into efferent lymph but also gain access to the blood vascular system by lymphaticovenous communications in nodes. Nevertheless the RLNs are biologically important and are unique from the rest of the lymphoreticular system. They are important in the initiation of tumor immunity. The RLNs are capable

of destroying tumor cells, and Fisher's studies indicate that the presence of negative nodes may be the results of such a circumstance as well as because tumor cells traverse nodes, rather than that a tumor has been removed prior to its dissemination.

More recently Fisher obtained evidence to indicate that RLN cells are instigators of a cascade of events giving rise to cytotoxic effector cells of both the lymphoid and myeloid series. RLN cells affect stem cells from which macrophages and granulocytes, which are also cytotoxic, are derived. He noted a decrease in macrophage production and cytotoxicity when RLNs are absent.(261)

Perturbation of the host by a variety of means, such as physical and psychic trauma, immune depression or antilymphocyte serum, can produce lethal metastases from cells which had been in peaceful coexistence with their host and without such interference would have remained so. Fisher then concluded that local recurrences following operation were apt to be the result of systemically disseminated cells lodging and growing at the site of trauma rather than because of inadequate surgical technique and that breast cancer is a systemic disease, probably from its inception.

Further studies showed that recurrence and survival were independent of the number of axillary nodes removed and examined, and that tumor location failed to influence prognosis.

In August 1971 a prospective randomized clinical trial was undertaken to confirm or deny the alternative hypothesis which Fisher had formulated. See Table below, reproduced from his report.

Two Divergent Hypotheses of Tumor Biology

Halstedian	Alternative
Tumors spread in an orderly defined manner based upon mechanical considerations.	There is no orderly pattern of tumor cell dissemination.
Tumor cells traverse lymphatics to lymph nodes by direct extension supporting *en bloc* dissection.	Tumor cells traverse lymphatics by embolization challenging the merit of *en bloc* dissection.
The positive lymph node is an indicator of tumor spread and is the instigator of disease.	The positive lymph node is an indicator of a host-tumor relationship which permits development of metastases rather the instigator of distant disease.
RLN's are barriers to the passage of tumor cells.	RLNs are ineffective as barriers to tumor cell spread.
RLN's are of anatomical importance.	RLN's are of biological importance.
The blood stream is of little significance as a route of tumor dissemination.	The blood stream is of considerable importance in tumor dissemination.
A tumor is autonomous of its host.	Complex host-tumor interrelationships affect every facet of the disease.
Operable breast cancer is a local-regional disease.	Operable breast cancer is a systemic disease.
The extent and nuances of operation are the dominant factors influencing patient outcome.	Variations in local-regional therapy are unlikely to substantially affect survival.

Reprinted with permission from B. Fisher: Cancer Research 40: 3863–3874. 1980.

This study involved more than 1,700 women who were followed 6 to 9 years. These women received three distinctly different regimens; a) radical mastectomy; b) total (simple) mastectomy and local-regional radiation; c) total mastectomy with removal of nodes only if they later became clinically positive. End results showed that in patients without clinical evidence of axillary node involvement *no significant difference in the overall incidence of first treatment failure, in the incidence of any first distant metastases or in survival*. Similarly in patients with clinical evidence of node involvement, treatment by radical mastectomy, or total mastectomy and local regional irradiation yielded no substantial difference.

The similarity in findings in patients with clinically negative nodes is remarkable considering that *40% of women subjected to total mastectomy alone had positive nodes*

unremoved and untreated. Those nodes could have been expected to serve as a source of further dissemination resulting in an increase in distant treatment failure. Of the 40% of patients with positive lymph nodes not removed, only 15% subsequently developed clinically positive nodes requiring an axillary dissection. These studies eliminated most of the considerations that might contraindicate the performance of breast conserving operations. Fisher also stated that *no* data are available to indicate that breast radiation is necessary or even desirable in all patients.

The finding that patients with putatively greater tumor burdens are better responders and that increasing the number of drugs may not necessarily improve results, suggests that current concepts may not necessarily improve results. In future we should design therapy for breast cancer based upon biological considerations rather than empiricism. *Thus patients and their treatment must now be grouped according to tumor-host biological properties rather than to clinical manifestations of the disease*. Fisher believes that clinical staging as we now know it will shortly become obsolete. In conclusion he stated that treatment will best be carried out by medical, surgical and radiation oncologists rather than by physicians having only a passing interest in breast cancer. Significant advances in breast cancer therapy are likely to result from a better understanding of the biology of the disease.(261)

Radical Mastectomy and Its Sequellae

More attention needs to be paid to the possibility of using less radical surgical procedures preceded and followed by immunotherapy. No one can deny that radical surgery entails, in addition to an increased operative mortality, really hideous mutilation.(446) Edema of the arm occurs three times more frequently in patients whose axillae have been dissected and this complication is very distressing indeed to the patient. Statistics show that in advanced cases the arguments in favor of the less radical approach are even more compelling.(594) It is impossible to escape the conclusion that radical surgery sometimes does more harm than good. When a particular form of radical therapy is widely practiced, the tendency has been to regard more moderate alternatives as suboptimal.

Leis believes it is time to stop discussing which operation is applicable to, or best for, every patient with breast cancer: "An operation should be performed on a selective basis, choosing for each individual patient a specific type of operation which affords a maximum of benefit and a minimum of trauma."(482)

The breast and ovaries have a very special psychosexual significance in the minds of most modern women. The impact of a mutilating operation such as radical mastectomy alone, usually stirs up an intense emotional reaction—a serious depression and a great sense of loss. Thus one of the most serious sequellae of radical mastectomy is the psychological impact. These patients have to cope with severe physical, psychological and social adjustments to the operation. These problems are dealt with at length in our section on Psychic Factors, Nursing and Rehabilitation. (see p. 117)

Prophylactic oophorectomy compounds this psychologic disturbance by adding a second major operation which may have a violent and disruptive effect upon the emotional stability of some women.(906) Since recent findings seem to downgrade the benefits of surgical oophorectomy, such operations are now being abandoned. Prolonged chemotherapy may produce the same effect without the trauma of a surgical procedure.(85)

Lymphedema: Treves (1921) was the first after Halsted to report on the management of lymphedema (the swollen arm) in carcinoma of the breast.(841) This is a very distressing

and sometimes disabling complication which occurs following mastectomy in up to 70% of patients. Haagensen decried this high rate of lymphedema, and said that in cases in which he personally supervised the postoperative care the incidence of disabling edema was very low.(345) Postoperative radiation, delay in wound healing, secondary infections, obesity and venous coagulation are all predisposing factors. The dangers of developing a swollen arm can be minimized by preventive measures at surgery.(704;899) The period of postoperative drainage should be reduced to a minimum.

Treves stated that gentle massage of the arm from the wrist to the insertion of the deltoid muscle will often relieve minor lymphedema. The use of pressure bandages applied while the arm is held above the head, and allowed to remain for several hours, tends to diminish swelling. Suspension of the arm may prove beneficial. The use of the Jobst elastic sleeve or of the Jobst pump have been advocated by a number of breast specialists.

Some surgeons at the Lahey Clinic believed that patients ideally should receive anti-coagulant therapy beginning three days after mastectomy if bleeding of the wound is considered to be controlled.(250) They found lymphedema may appear in 85% of patients with grade II to IV carcinoma. Venography invariably showed the brachial and axillary veins were obstructed. *These cleared in half the patients given fibrinolysin as proved by venogram.*

Overexercise induces lymphedema. Some surgeons bandage the arms of their mastectomy patients with elastoplast for eight weeks to prevent lymphedema. Lymphedema of long standing is highly resistant to treatment. Rydell et al used Habif's method: the patient is hospitalized for five days and each day 50cc. of a mixture of one ampoule of hyaluronidase in normal saline is injected into the subcutaneous stratum of the entire arm, 5cc. being introduced at 10 sites 5 cm. apart. The entire arm is then encased in a compression dressing and elevated for three hours. This may be repeated at the discretion of the physician in one to two months. All obese patients should be encouraged to reduce their weight.(723)

Robbins and Markel believe all available *preventive* measures should be utilized since medical and surgical procedures are not very effective once it has developed. The use of elastic sleeves and pressure pumps may be beneficial. A low salt diet and the use of diuretics may also be helpful.(704) Smedel and Evans found a swollen arm in 57.5% of all patients seen at the Lahey Clinic who had radical mastectomy alone in 1953. Of those who also had radiation 85% had lymphedema.(763) By 1973 Robbins believed lymphedema caused serious problems in only 10% of patients.

Treves in analyzing over 1,000 cases of lymphedema seen at Memorial Hospital prior to 1957 stated that 42% of the cases receiving radiation developed it, but only 16% of those treated by surgery alone. Predisposing factors were the presence of positive axillary nodes, delayed wound healing, secondary infections, obesity and venous angulation. Men are less prone to develop it than women. Treves' preventive measures included: "Reducing the period of postoperative drainage to a minimum. Necrosis of skin edges may be eliminated if serum does not collect in the axilla, since the collection of fluid separates the flaps and interferes with the blood supply. Obliteration of the axillary dead space should be avoided. The use of preoperative radiation should be discontinued and postoperative radiation should be judiciously employed in doses that minimize the complication attendant on its use . . . The obese patient should be convinced to diet in order to reduce her weight to the crucial 150 pounds."(843)

The onset of swelling in patients previously free from this complication may be initiated by many different minor infections or trauma, friction from clothing, trauma to the arm, a scratch or a mosquito bite, or a minor cut or thermal injury, or ringworm of the nail.

Any of these may produce lymphedema which endures. The circulatory balance is so fine that seemingly trivial incidents may produce this distressing complication, and once produced the process is rarely reversible. The care of the hand and arm on the operated side should be an important part of follow up.

These suggestions should be given to patients after mastectomy:(704)

1. Push cuticles back—do not cut— avoid possible infection.
2. Wear canvas gloves when gardening; wear rubber gloves when cleaning pots and pans with steel wool.
3. Wear padded gloves when reaching into oven. Avoid burns.
4. Keep watch band and jewelry loose on operative arm.
5. Keep dress sleeves loose. Avoid pressure and swelling.
6. Use unaffected arm to carry heavy purse and packages.
7. Use unaffected arm for blood pressure readings, injections, etc.
8. Wear thimble when sewing.
9. Wash the smallest break in the skin on operative side immediately with soap and water, and cover with a bandaid.
10. Use electric razor for shaving and avoid nicks and scrapes.
11. Do not get sunburned, get tanned gradually.
12. Contact doctor if arm on operative side feels hot, is reddened or swollen.
13. Try to give up smoking, but if you do smoke, hold cigarette in the unaffected hand—avoid possible burns.
14. Keep affected arm elevated when sitting; do not let arm hang down by side.

Nerve Entrapments: Another complication which may occur after radical surgery for breast cancer is nerve entrapment, which may be responsible for the numbness, paresthesia, weakness and pain of the arm. Lymphedema of varying degrees found in 50% of patients was associated with brachial plexus entrapment and carpal tunnel syndrome. These two should be added to the list of complications following mastectomy, with lymphedema playing an active part in their development.(302)

Lymphangiosarcoma: This is a very malignant tumor of lymphatic vessels usually arising in a limb that is the site of chronic lymphedema.(200;382;790;819) Most of these tumors occurred in breast cancer patients who had had a radical mastectomy up to 24 years previously.(790) It is relatively uncommon. The discomfort and uselessness of the edematous arm may be seriously complicated by the development of this soft tissue sarcoma which is aggressive and not only metastasizes widely, but also recurs locally within the fields of irradiation, following temporary regression. Interscapulothoracic amputation fails to control the disease except in very rare instances.

McSwain et al cautioned that in any patient with a swollen arm a blue, red or purple spot should be considered lymphangiosarcoma and promptly excised locally or biopsied for microscopic examination. Then radical wide excision, including the underlying muscle sheath, should be done for small superficial lesions.(527)

Since 1948 over 35 reports have appeared totalling over 135 cases. (200;280;381;382;521;527;763;776;914) This highly malignant vascular soft tissue sarcoma has occurred in men as well as women. It has been treated by radiotherapy with poor results. Radiation may produce regression, but it is usually short lived and in some cases seemed to have a deleterious effect. Herrman reported a five year survival in a

patient who received both external radiation and intra-arterial injections of radioactive ytrium microspheres. However, this treatment caused intense long lasting pain in the limb, persistent edema of the fingers and hand and impaired hand function.(382) The mean survival after onset ranges from 16.8 months after amputation and 18.5 months after radiation.(382;676) At least 13 cases have survived five or more years.(200;280;776;914) Woodward et al believed that early recognition of the lesion and prompt ablative surgery seem to offer the best chance of survival.(914)

The Potential Role of Immunotherapy in the Prevention and Treatment of Lymphedema and Lymphangiosarcoma: It is interesting to note that none of the patients developed lymphedema who received injections of mixed bacterial vaccines following breast surgery, (see below Part III, Series 1–5), their disease free survival period was remarkable, and no patient so treated developed a secondary primary such as lymphangiosarcoma.

Bacterial vaccines stimulate host resistance, including the production of endogeneous interferon and prostacyclin. This results in pain relief, rapid wound healing and regeneration of tissues destroyed by the tumor.

Klein treated one case of lymphangiosarcoma with immunotherapy and chemotherapy, achieving a six year remission before the disease reactivated. Very few of these cases treated by amputation, radiation or chemotherapy survive more than two or three years. (Personal communications from E. Klein.)

Phantom Breast Syndrome: Patients who have had a radical mastectomy often develop the so called phantom breast syndrome, that is they feel that their amputated breast is still there.

Amboise Paré is quoted as being the first to mention the phantom breast about 1550.(182) Crone-Munzerbrock found that 26 of 49 radically mastectomized women had breast phantoms varying from complete sensation of the whole breast to feeling the nipple only. It occurred at varying times, precipitated mainly by weather changes, particularly by the cold. Only three patients ascribed it to emotional excitation, six felt it only at menstruation, with swelling and tightness of the phantom. In one it disappeared at menopause. About 25% also had pain in the phantom, for which no peripheral cause could be found. In eight patients pain radiated to the nipple.(182)

This syndrome is unrecognized by many physicians, yet it poses serious problems for many mastectomy patients. Jamison's study indicates that there is a need for increasing awareness on the part of the medical profession for simple preventive efforts that may aid physicians in their postoperative treatment of these patients.(424a) Most women do not report these symptoms to their physicians, despite their severity. Women who experienced P.B.S. feel that they did not receive much emotional support from their surgeons and that most of their emotional problems were secondary to the mastectomy. In these respects they differed from women who did not have P.B.S.

Younger women seem to complain of this syndrome significantly more often. Probably the psychological factors are more important than the physical factors in causing the syndrome. The loss of the breast may come at a time when the women is not psychologically prepared to deal with the losses that aging brings. The postmenopausal woman may be better prepared to accept the inevitable and gradual changes.

Women who have a better relationship with their spouse have a significantly lower incidence of P.B.S. Patients with good interpersonal relationships tend to focus less on physical symptoms and recover more quickly from surgery.

The presence of a phantom with or without pain can only be construed as a way of handling the loss of a part of the body. It represents a kind of mourning for a part which, like normal mourning for a person, may get out of hand, i.e. result in a severe depression, in this instance represented by a phantom, with or without pain.

In neurotic women the breast becomes overinvested, i.e. excessive pride or shame. It may be equated with the penis—the breast being a woman's main visible feminine attribute. The phantom represents an attempt to deny the loss, thereby denying the anxiety associated with the loss, i.e. castration.

Surgeons seem to expect women to accept surgery on their sexual organs much more readily than they do men. The feeling about surgery of the sexual organs are, of course, carried over into attitudes toward the breast as a part of the sexual apparatus. (See below, pp. 195–202)

There is a great need for emotional support in the postmastectomy period. One of the most important findings is the significantly decreased incidence of P.B.S. in women who receive strong emotional support from the surgeon. Thus surgeons themselves hold an important key to preventing this syndrome. It indicates the need for public knowledge and professional education. Many surgeons fear that such discussions may suggest symptoms to patients who would otherwise not experience them. Jamison's study indicates exactly the opposite.(424a)

***Costs of Radical Surgery*:** In the aggregate, radical mastectomy is no more effective than simple surgery in terms of survival, or the chances of distant recurrence. It does, however, cost the American woman more in dollars for surgery and hospital expenses and it induces more morbidity, more mutilation and more traumatic psychological adjustment, as well as carrying a greater risk of surgical death.(108)

McPherson and Fox, in a provocative discussion of the treatment of breast cancer, concluded that these extra costs and risks ought to be justified by some equivalent benefit. For instance, in Massachusetts in 1973 the mean fee paid for the Medicare population for simple mastectomy was $232, with a range of $100 to $500. For radical mastectomy, equivalent figures were $412, and $300 to $900. In the United States as a whole in 1972 the average hospital stay for simple mastectomy was six days and for radical 10.3 days. The costs therefore for surgery and hospital for simple mastectomy was $1,500; for radical $2,600. These are conservative figures. New York breast surgeons charge much more. With approximately 90,000 new diagnoses each year, the difference between these two procedures represents more than $100,000,000 per year.(108)

***The Need for More Conservative Approaches*:** In conclusion they stated: "A more comprehensive view of breast cancer must be sought in the hope of identifying more effective ways to intervene. In the meantime we must learn how to modulate therapeutic intervention whose justification appears to reside in beliefs held both by the patient and physician. The transition from the circumstance in which strategy is based on belief to one in which it is based on fact will no doubt be difficult."(108)

McPherson and Fox further stated: "The intuitive notion that the maximum purging of possibly offensive tissue is the most effective approach to the treatment of breast cancer, and of cancer in general, continues to dominate the medical procedure. . . there is little, if any, evidence to support it.(526)

The possibility that the response of the lymph nodes adjacent to the breast provides a substantial component of the immune response against the tumor itself and perhaps to its metastases gives rise to the hypothesis that *treatment of these nodes (ablation or radiation) might cripple this component of the response.*(263)

Conservative Surgery, Alone or Combined with Radiation

Despite the very serious late effects described above there continue to be breast cancer surgeons such as Urban who firmly believe that radical mastectomy is the method of choice.(705;852) However, more and more surgeons are expressing doubts as to the wisdom of eradicating all accessible lymph drainage areas. "The possibility of lymph nodes being actual brakes in the spread of the disease is gaining increasing evidence. Add to these unresolved doubts the greatly increased mutilation and the increased mortality and morbidity of supra-radical surgery, and it will surely be appreciated that an alternative approach is at any rate worthy of consideration."(673)

A more conservative approach is no new conception. Keynes was the first in 1927.(449) *He performed simple excisions followed by diathermy and/or radium.* After 24 years' experience he concluded that the treatment of breast cancer may justifiably be much more conservative provided the necessary prophylactic treatment is used.(449)

In discussing the need for more conservative surgery in 1937 Keynes stated: ". . . it must be the ambition of every conscientious surgeon to help in the gradual elimination of any operative procedure so extensive and severe as the radical operation for cancer of the breast. . . . No one can deny that radical surgery entails . . . a really hideous mutilation. . . . Routine radical surgery does apparently sometimes result in actual dissemination of the disease and widespread recurrences in the skin flaps and their surroundings. It is impossible to escape the conclusion that radical surgery sometimes does more harm than good. Finally, and I believe, very importantly, there is the psychologic aspect. Most women know what is meant by surgical treatment of cancer of the breast, and I am sure that very often they are intimidated by the prospect. . . . *very often hiding their disease until two years or more have elapsed since it was first noticed.*"(447) See below section on Radiation for a description of Keynes' pioneer use of this modality alone or combined with conservative surgery.

In spite of Keynes' widely published views on this important subject, they were almost universally ignored by the majority of breast cancer surgeons who preferred to "follow a surgical dogma, however irrational it might be shown to be, rather than making the effort to regard each patient as a separate problem for treatment best suited to her individual case."(449)

Keynes noted in 1981 that over the past 30 years he has watched the pendulum swing against the dogma of radical mastectomy. "The curious reluctance to face the facts is at last giving way before a tide of common sense in favor of more rational treatment."(449)

Rubens Duval in 1930 was the first in France to urge more careful collaboration between surgeons and pathologists during breast cancer surgery to avoid unnecessary mutilating operations for relatively benign lesions.(718a)

In 1940 the surgeons of the Southeastern region of Scotland changed to *simple mastectomy and radiotherapy* as the preferred treatment, having condemned the radical operation.(101) This new Edinburgh policy occasioned great disquiet and much hostility, and this adverse criticism led Bruce and his colleagues to analyze their end results. They then undertook a randomized clinical trial and by March 1969, 395 cases had been distributed: 191 to simple mastectomy and radiotherapy and 204 to radical mastectomy.

In reporting this study in 1971 Bruce stated that there was no statistically significant difference in survival between the two groups.(101)

Murley, one of Keynes' students at St. Bartholomew's Hospital in London, did appreciate the value of Keynes' approach.(418;901) *In 1956 he noted that results are more closely related to the aggressiveness of the tumor and resistance of the host than to the conditions of treatment.* He added that it was regrettable that survival rate is often considered to the exclusion of the mutilation and morbidity of the more radical operations. Edema of the arm is three times as frequent in patients whose axillae have been dissected. Statistics show that in the advanced cases the arguments in favor of the less radical approach are even more compelling.

Turner et al reported in 1981 on a prospective randomized trial (534 patients, 1969–1976) designed to determine whether radical mastectomy conferred advantages over the modified radical procedure in terms of total survival, local recurrence, distant metastasis and disease free interval. The results showed no significant difference in outcome as regards these variables between the two treatments.(848)

Roses et al, 1981, reported on a technique for total mastectomy with complete axillary dissection, which uses division of the insertion of the sternal portion of the pectoralis major muscle, preservation of its innervation, reconstruction after completion of the dissection and resection of the pectoralis minor muscle. This has been evaluated in 115 consecutive cases. Such a modification facilitates a thorough axillary dissection, while preserving the cosmetic and functional benefits of the Patey operation.(715)

Vera Peters was the pioneer in Canada beginning in 1939 in doing a comparative study of the end results following local wedge resection and radiation versus mastectomy and radiation.(665;666) She found this as effective as any other treatment for Stage I and II breast cancers. By 1969, 217 patients had been treated in each group matched by age, size of primary and year treated. Of these, 72 pairs were excluded due to death from extraneous causes under 10 years. In the excision group better survival occurred in all ages up to 60. Beyond that no difference was seen.

In her series 63 pairs had T1 primaries 2 cm or less. No survival differences occurred between the conservative or the mastectomy groups; 82 pairs had T2 primaries (average 3.2–3.5 cm). Peters stated: "This group advances the most dramatic difference in the entire study! Survival was much higher in those conservatively treated. In those treated by *mastectomy*, the lower survival and higher metastatic rate in bulkier T2 disease suggests this procedure to be a hazard, setting loose the increased load of malignant cells to circulate, by which metastases could be born. However, the *gentler technique of excision* permits the patient to remain normally active, and relatively untraumatized, leaving the circulating malignant cells less likely to become enmeshed in traps set by systemic changes which are promoted by prolonged periods of shock."(666)

In conclusion Peters stated: "The quintessence of our profession is that of strengthening the quality of life. . . No woman in true clinical Stage I breast cancer should fall victim to the mental anguish or physical morbidity of radical ways. . . . This study shows what I have long known to be true: that radical methods are not in the best interests of the patient." Peters believed that prophylactic mastectomy could with few exceptions be eliminated in early breast cancer relying on wide primary excision.(666)

Next came the work of Mustcallio in Finland(599;600) and Crile in Cleveland.(174–181) Crile, in 1974 reported that the 10 year survival rate for patients treated at the Cleveland Clinic by less than radical mastectomy was the same as that in the National Registry in similarly staged patients treated by the radical procedure.(178;181) He concluded: "*Today it is women's fear of the operation that is responsible for most of the*

delay in seeking treatment. When the standard radical operation is abolished, I believe women with breast cancer will come earlier for treatment and their chances of survival will be improved.''(178)

In 1945 Mustakallio and his colleagues in Helsinki first expressed the belief that mammary cancer must be regarded from a very early beginning as a general disease and that the patient's fate is decided chiefly by her own cancer resisting powers. They concluded that every effort must therefore be made to reinforce host resistance, and that radical surgical procedures and large doses of radiation should be avoided.(600) They therefore began using lumpectomy combined with postoperative radiation and achieved 84% five year survival.(599)

A later larger series of 791 cases showed a five year survival of 70%.(600) Rissanen, who continued the program, reported in 1969 on 1,008 cases of Stage I breast cancer of which 415 were treated by conservative surgery plus postoperative orthovoltage radiation and 593 received radical mastectomy plus radiotherapy.(702) The five and ten year survival rates for the conservative group were 70 and 71%, while for the radical surgery group they were 82 and 71.5%. These differences were not statistically significant. A local recurrence developed in 25% of the women treated conservatively but this was managed by a new operation and radiotherapy.

Complications were markedly less frequent with the conservative operation: 6.7 versus 32% lymphedema of the arm; limited arm movements, 3.1 versus 16.7%; pain in the shoulder joint, 6 versus 15%.(701;702) These excellent results may be partly attributed to the host stimulating effects of the traditional hot sauna baths so widely used in Finland.(608)

Forrest and his colleagues in Edinburgh commented on the need to consider the place of alternative forms of local therapy, particularly in those whose ''mini-tumors'' are detected through screening programs. *Local excision of the primary tumor, prosthetic replacement following simple or modified mastectomy and primary local radiotherapy* are all methods which spare mutilation and morbidity and which require to be assessed more widely through well controlled cooperative studies.(286;287) They urged that all who treat breast cancer be prepared to include their patients in such trials in their region or country.

At the International Cancer Congress in Florence (1974) Hayward, Surgical Director of Guy's Hospital Breast Unit was one of many who criticized the extirpation of lymph nodes. Several other speakers stated that a negative node in a region draining a tumor is an asset rather than a liability. ''That it was not invaded,'' Denoix pointed out, ''does not mean that it had not been assaulted by malignancy, but rather that it had been able to throw off the tumorous attack.'' This concept, said the UICC President, is a new trend espoused by the younger surgeons ''who have more open minds and fewer bad habits than the older surgeons.''(371)

In the same year another Scottish group reported evidence which lends support to the current proposals of limiting primary treatment of operable breast cancer to simple mastectomy alone plus determination of the state of the axillary nodes at the primary operation—''*a simple and sample approach.*''(355) Despite adverse criticism, McWhirter reemphasized ''that meddlesome, invasive surgery in the involved axilla is a hazard to the patient.''(259;267;529) The Edinburgh school now has a large series treated by simple mastectomy and tolerance dosage (3750r) of deep X-ray.(528;529)

Prosnitz et al reported on a cooperative study at four centers—Yale, Harvard, Jefferson and Hahnemann Medical Schools with 150 patients receiving *radiotherapy following excisional biopsy*. Their results were comparable with those of conservative surgery. They

concluded that mastectomy is not a necessary part of the treatment of small cancers of the breast, that radiation without mastectomy is an acceptable alternative with far superior cosmetic and functional results.(684)

The surgeons in the U.S.S.R. have favored conservative measures since 1954.(673)

Comparative End Results

Meyer et al analyzed 1,686 surgically treated breast carcinomas and found no significant differences in five and ten year survival for simple, modified radical, or radical mastectomy.(560)

Baker et al at Johns Hopkins compared the results of modified radical mastectomy (114 cases) with radical mastectomy (188 cases) in the treatment of operable breast cancer. Of these 205 had Stage I, 60 Stage II and 67 Stage III disease (TNM system.) There was no statistically significant difference in five year survival when results of these two procedures were compared at any stage of the disease.(31) A modified radical mastectomy takes longer to perform than the radical procedure.

In Boston, Cope et al reported on a 20 year study of limited surgical excision as the basis of comprehensive surgery for breast cancer.(168) In 10 patients with tumors which were "non-invasive or sluggishly so," no further treatment was given. In the other 121 cases patients received 4,000 to 5,000r to the residual breast and the adjacent lymphatics received a tumoricidal dose of 4,000 to 5,000r. Since 1971 the area of surgery and residual breast has subsequently received an additional 2,000 to 3,000r from 192 Iridium, using interstitial needles or electron beam from the Betatron. In 12 of the 121 cases prolonged chemotherapy survival rates to date compare favorably with those treated by radical mastectomy.(168)

The M. D. Anderson group in Houston reported excellent control of local and regional tumor (96%) with "conservation surgery" combined with radiation.(582)

Vilcoq et al at the Fondation Curie in Paris reported in 1981 on end results in 314 patients treated for a localized breast cancer by tumorectomy and radiotherapy.(861) The five year survival free of disease was 84%. Cosmetic results were excellent in 90% of the patients. They concluded this combination is an acceptable alternative to mastectomy, particularly since salvage surgery can usually be successfully performed for the recurrences. These were common in young patients. No patient older than 50 had recurrence.

By 1978 Alpert et al had treated 109 cases by tumorectomy and radiotherapy or radiotherapy alone. Almost 30% with small tumors were considered inoperable for medical reasons and 70% refused mastectomy.(12) (The number of patients refusing mastectomy has increased since 1973.) Microscopic involvement of the surgical margin by cancer did not alter the local control rate. The cosmetic results were good in 98% of the patients. They concluded that gross removal of the tumor followed by radiotherapy may be offered as an alternative to mastectomy in these patients.(12)

Multicentric microfoci of cancer are often present in patients with breast cancer and affect the contralateral breast as well. Despite the high incidence of these microfoci, the appearance of new clinical cancers is rare. In a period of 610 patient years after partial mastectomy, the danger of the appearance of a new cancer in the affected breast was less than might have been anticipated.(177)

Segmental resection (also known as partial mastectomy, lumpectomy or tylectomy) has been reported to be equivalent to radical or modified radical mastectomy in terms of

five and ten year survival.(173–180;598;599;665;666) However these studies were mainly retrospective and the problem still remains controversial.

The National Surgical Adjuvant Breast project is currently comparing the role of segmental mastectomy with and without radiation to modified radical mastectomy. Should this prospective trial prove that survival following segmental resection is equivalent to modified or radical mastectomy the gain for patients in cosmetic appearance and alleviation of psychosocial problems that women endure will be gratifying.

However, improperly performed segmental operations give unsatisfactory cosmetic results and weaken the case for this procedure. Margolese describes the technique which can avoid poor cosmesis in patients for which this method is suitable.(544) Clearly there will be patients with breast too small, tumors too central or too large to be handled in this way. Nevertheless, from the technical aspect, most breast cancers can be adequately handled by this approach, with acceptable, even excellent cosmetic results. There is mounting evidence that a partial or segmental operation may be as effective for long-term control as total mastectomy. To obtain conclusive proof, more surgeons must be encouraged to enter patients into the prospective clinical trials in Europe and North America which are now in progress.(544)

Wertheim and Ozzello found nipple involvement in 23.4% of 1,000 mastectomy specimens.(895) Quinn and Barlow found involvement of the nipple or areola in 25% of a smaller series of mastectomy specimens.(686) These studies underscore the definite risk of recurrence after surgical procedures that preserve the nipple including banking it for future breast reconstruction.

Adami et al in Sweden reported on survival after selective treatment for brest carcinoma in 110 patients. They concluded that patients without axillary metastases can reliably be selected by exploration of the axilla with lymph node biopsy and preoperative cytological examination and that in this group simple mastectomy results in a high disease free survival (95%.)

Roberts et al reported on the Cardiff breast trial of simple vs. radical mastectomy. By the end of 1973, 230 patients had been admitted to this trial. By 1972 there was nothing to suggest that the conservative approach (simple mastectomy) was inferior to the radical one.(708)

Kaae reported on the Danish randomized trial (1951–1957) and found there was no difference in the 5, 10 and 15 year survival of the patients given simple mastectomy plus postoperative radiation and those given extended radical mastectomy.(433)

Conservative Surgery without Radiation

In 1972 the Royal Marsden Hospital began a pilot study designed to test the hypothesis that with a negative node status minimal surgery and *conservation of the breast is indicated with no other therapy*.(333) By 1981 a total of 75 patients had been followed up to 9½ years and 89% were alive, four had died of cancer, four from other causes, one lost to follow up. (Personal communication from W. P. Greening, December 1981.) The 5 to 9½ year survival rate was 84%.

The indications they used were: a) the tumor was located in the outer half of the breast, was less than 2 cm. in diameter in the excised specimen; b) on clinical examination there was no involvement of the skin overlying the tumor, with minimal tethering never measuring more than 2 cm; c) negative axillary nodes on clinical examination, confirmed by histology.

Cooperative Trials

***Cooperative Trials in England*:** In England a multicenter prospective trial was undertaken in 1970 to compare the effects of simple mastectomy plus radiotherapy versus simple mastectomy alone for Stage I and II breast cancer. By 1972 Edwards et al reported that 1,050 patients had been entered. An interesting finding was that axillary nodes had regressed within three months in 75% of patients with clinical Stage II carcinoma. They believed this spontaneous regression of the nodes might be due to resolution of reactive changes in lymph nodes following removal of the primary.(239)

At five years there was no evidence that routine postoperative radiotherapy was harmful or that it conferred further benefit as regards survival or incidence of distant metastases. Radiotherapy did reduce the incidence of local recurrence. Neither form of treatment can counter occult disease that is present far from the breast at the time of initial therapy, but the results of this study support the view that conservative primary treatment and subsequent chemo-immunotherapy may be the treatment of choice in the future.(597)

***The Patient's Options*:** Hugh Auchincloss has recently very ably expressed a surgeon's views of the patient's options on treatment for breast cancer.(25) He believes that "for women who rely implicitly on the advice of their doctor, ask few questions and want him to decide, the recommended treatment should be modified radical mastectomy."

Women who want to have a role in the decision-making should be given as much information by her surgeon as exists as to the available options. If they then opt for conservative treatment they should receive it. By so doing they must also be prepared to accept a large share of the responsibility for choosing a form of treatment which, in his opinion, has not yet been widely established as having as high a 10 year cure rate as occurs with modified radical mastectomy.(25)

***Cooperative Trials, U.S.A.*:** As regards the great importance of cooperative trials, Fisher stated in 1971: "It is my belief, and I cannot emphasize it too strongly, that at the present time it is the obligation of any surgeon who is performing breast cancer surgery in an institution capable of carrying out clinical trials as part of a cooperative group, to participate in such a program. Teaching hospitals, clinics and cancer institutes are all particularly suited for such an undertaking. The National Surgical Adjuvant Breast Project has been established for such a purpose.* It provides the opportunity for such cooperative endeavors having as their objective the clinical evaluation of the worth of certain modalities already employed and those which may, in conjunction with surgery, improve results. Those institutions whose members recognize the urgency of such an effort are invited to participate."(260)

In 1977 Fisher et al published their first report on the prospective randomized clinical trial comparing radical mastectomy with alternative treatments for primary breast cancer. Results failed to demonstrate an advantage for those patients who had a radical mastectomy. They reported that leaving behind positive axillary nodes has not as yet increased the incidence of distant metastases in the overall proportion of treatment failures.(270)

Cautionary Note: No matter what is done surgically for carcinoma of the breast, it must be done with gentleness, gentleness in handling the tissues, gentleness in touch, and that applies to the physical examination as well as the preparation of the operative field. H. W. Meyer noted that he had seen nurses in an operating room prepare a breast

*The NSABP was started in 1958 and in the next 23 years about 10,000 women have been included in the various protocols. (B. Fisher, personal communication, 1981.)

in such a way that he was horrified because he could imagine those tumor cells being spread by embolism by the rough rubbing over the breast.(424)

Breast Reconstruction

Reconstruction following removal of a breast has now become acceptable adjuvant therapy during primary treatment of breast cancer.* No longer is survival free of disease the only standard whereby success of breast cancer treatment is measured. Quality of life and body image integrity are now also important considerations in management.(305) To meet this need, an increasing number of breast cancer surgeons and plastic surgeons have been reconstructing the breast following mastectomy. These replacements are carried out either as a primary or a delayed procedure.(305)

Ward believed that if the public were more completely informed, those women for whom the dread of mastectomy was greater than the fear of cancer itself would seek earlier treatment.(872) Ward noted that preparation of the patient for breast reconstruction must take more time than is usually allotted in the outpatient department. Whether immediate or delayed reconstruction is planned, she should know what this implies in terms of scars and have an idea of final results from photographs or reprints.(872) Possible hazards or disappointments should be recognized. Discussion with a woman who had completed such surgery is the best solution—an added role for the Reach to Recovery program in the United States or the Mastectomy Association in England.

Leis found that discussing the possibility of breast reconstruction is valuable for the patient about to undergo breast biopsy who may need some form of mastectomy. Many patients, adamant in refusing to have their breast removed, have agreed to modified radical mastectomy once told that later reconstruction might be possible. After mastectomy and an adjustment period, however, many women no longer want reconstruction.(482)

It would seem that the psychic effects of reconstruction may have beneficial effects on the host resistance of the patient and thus make recurrence *less* likely to occur. Breast reconstruction in selected cases has become an accepted part of rehabilitation.(585)

An experienced French group recommends breast reconstruction only to patients who have had no irradiation, and have a satisfactory prognosis, at least two years after the initial surgery. This is because analysis of the psychological problems shows that cancer remains the patient's dominant preoccupation, often masked by the mutilation. (See below, section on Psychological Adjustment, page 117.) This fixation on mutilation often appears to be a defense mechanism against fear of death. The depth of despair of these patients in cases of recurrence after reconstruction can readily be imagined.(667) When reconstruction is not successful, severe stress also occurs.

Local recurrence of breast cancer around prosthetic implants has largely the same significance as it does in a non-reconstructed chest wall. It tends to be a harbinger of systemic metastases. Der Hagopian, et al found it was not necessary to remove the implant either for local control or for complications of treatment.(201a)

Selection of cases and choice of technique are important. The patient's age and health, and the need for keeping the number of operative stages at an absolute minimum are of great importance. One must be sure that the proposed reconstruction is of such a nature that it can reasonably be endured by the patient. Multi-stage operations necessitating several admissions and anesthetics, especially in patients who are frail or not in the best

*NOTE: The distinguished Heidelberg surgeon and investigator, Vincent Czerny (1842–1916) is generally credited with the first attempt at breast reconstruction in 1895.(186) He transplanted "a lipoma larger than a fist from her right lumbar region to reconstruct the extirpated breast. This procedure was entirely successful."(324)

of health, may not be in their best interest, whereas a single stage procedure could be entirely acceptable.

When the skin of the anterior chest wall is excessively light, badly scarred, too thin or if it has been irradiated or skin grafted, then it is inevitably unsuitable as coverage for an implant.(667) The problem is then overcome by the replacement or supplementation of the inadequate skin by transference of a skin flap from adjoining tissue. Equally important is meticulous dissection technique, hemostasis and planning of incisions together with preservation of the blood supply and gentle handling of the tissues to prevent flap necrosis.(58;59)

Modified radical mastectomy lends itself well to simple reconstructive procedures in most cases. With newer techniques in plastic surgery some of the more radical defects can also be reconstructed in a single stage procedure using a latissmus dorsi musculocutaneous flap. The operation usually takes two to three hours and patients remain hospitalized for five to seven days. They may return to work within three weeks but should refrain from heavy physical exercise of the involved arm for six to eight weeks.(720)

Birnbaum and Olsen describe procedures for total breast reconstruction in patients who have had radical or modified radical mastectomies including restoration of the contour of the breast including the nipple areola complex and filling the defect from the loss of the pectoral muscles. By 1978 this had been accomplished in 37 cases with good results.(58–60)

Birnbaum uses dermal grafts for the reinforcement of the cover over implants in breast reconstruction after radical mastectomy. He removes the epidermis and superficial dermis from just above the buttock fold. The underlying fat is left behind. By carefully selecting the patients, they feel this relatively minor procedure may replace the use of distant flaps in a good many breast reconstructions.(58)

***End Results of Reconstruction*:** Local recurrence appears to be somewhat less frequent than one would expect. When it occurs, it can be treated by radiation, excision, or immunotherapy and chemotherapy, without removal of the prosthesis.

Watts et al recently reported an 87% seven-year survival in a series of Stage I and II breast cancer patients treated by mastectomy and primary breast reconstruction, using silicone prosthesis.(879) The results of this combined surgical procedure are comparable with those achieved by radical mastectomy, simple mastectomy, or local excision and radiation. Sub-prosthetic recurrence did not appear to be a problem. There was no recurrence of growth due to preservation of the nipple which was done whenever the tumor was not directly invading this structure. In one case Paget's disease developed as a late complication, but responded easily to irradiation and did not recur.(879)

In over 450 breast reconstructions which Birnbaum had performed by 1981 only two patients have developed metastases in reconstructed breasts over three years after their mastectomy. Two other patients developed distant metastases. He waits a minimum of three months after mastectomy before doing breast reconstruction. The main decision however is determined by the surgeon or oncologist in charge of the patient. (Birnbaum, personal communication, November 1981.)

Multicentric Breast Cancer

Women with a single site and single type of carcinoma have a better prognosis (2.5% mortality per year) than those with multiple sites and multiple types (15% mortality per

year) even though the stage of the disease may be similar. When the latter groups contained a scirrhous type duct carcinoma, the annual mortality rate approached 25%.(240)

Surgery for Bilateral Breast Cancer, Incidence and Mortality

A recent study of data from the National Surgical Adjuvant Breast Cancer Project on 2,734 patients who had radical mastectomies for Stage I or II carcinoma, revealed that 52 (1.9%) developed a new tumor in the other breast. Only 25% of these were the same cell type as the first cancer. The survival rate for these patients was no worse than for those who never developed bilateral disease. Thus, the maximum rate of improvement of five-year survival by routinely removing the other breast would be only 0.8%.(762)

Robbins and Berg reported from Memorial Sloan-Kettering Cancer Center that a woman has a five-fold increased risk of developing cancer in the other breast if she has had one in the first.(707) In their prospective 20 year study of 1,458 cases, 94 (6.5%) developed a second primary in the contralateral breast. The incidence over the years averaged seven cases per year per 1,000 patients. The observed 20 year survival rate was 27%. Women under the age of 50 at first mastectomy had twice the yearly risk of those over 60. Women with low grade ductal carcinoma had a significantly lower risk, while those with comedo and lobular carcinoma had significantly higher risks.* The highest incidence were women who had multiple cancers in the first breast. Incidence rates are modified by factors affecting prognosis. Second cancers were smaller than the first and had fewer node metastases. They tended to resemble the first cancers in type.

Harris et al studied familial breast cancer as regards bilateral cases. They found that in patients with a family history of breast cancer, the cumulative risk to the contralateral breast increased annually by 2.8% in the first six postoperative years, then showed no increase in the next seven years, and finally resumed its upward climb at an accentuated rate of 6.8% between years 13 and 16 inclusive. It is likely that tumors manifested in the contralateral breast within six years were already developing but not clinically discernible at the time of the first mastectomy. In contrast the extended disease-free period of many patients suggests that host defence mechanisms may have been stimulated by the first tumor thus having a persisting suppressive effect on de novo carcinogenesis in the contralateral breast. Their findings indicate the need for vigorous follow up of long term survivors of an initial breast cancer, particularly in familial cases.(365)

McCredie et al reported on the incidence of consecutive primary carcinoma of the breast in 1,489 women in London, Ontario as being only 1% per year for 20 years. The age of the women with bilateral carcinomas was six years younger than those with single tumors. They found the survival of women under 50 tended to be better. Patients who developed metastases had a shorter interval between their first and second tumors than those who had remained free from disease. They also stressed the importance of carefully observing the second breast, especially in younger women.(522)

Mueller and Ames reviewed the frequency and mortality of bilateral breast carcinoma in the Upstate Medical Center Cancer Registry at Syracuse, New York from 1956–1978. They concluded that carcinoma of the second breast occurs at a steady rate of slightly less than 1% per year. However, development of the second carcinoma does not significantly enhance the lethality of the first breast cancer and survival curves do not show an increased rate of dying due to the second cancer. In their study, half of the women with bilateral carcinoma are dead within 10 years after diagnosis of the first cancer.(593)

*True lobular carcinoma in situ occurs bilaterally in 25–30% of cases and indicates a considerable risk for the remaining breast in the individual.

***Risk Factors*:** In summary, women at greatest risk of developing bilateral cancer in the contralateral breast are: a) under 50 years of age at first mastectomy.(707) However, McCredie et al found that the survival rate for women under 50 tended to be better;(522) b) Familial history of breast cancer; c) those with multicentric or multiple primaries in the first breast;(707) d) those with comedo or lobular carcinomas;(707) e) those exposed bilaterally to radiation for benign lesions or for diagnostic purposes.(601)

***Precautionary Measures*:** Lewison believes that periodic physical examinations supplemented by mammography and other meaningful diagnostic aids (thermography, xerodiography and ultrasonography) are to be preferred to random biopsy or prophylactic mastectomy of the asymptomatic contralateral breast.(498)

Leis believes that only if the patient is in a "high risk" group for developing primary contralateral breast cancer is prophylactic delayed simple mastectomy of the remaining breast advised. In 91 cases where this was done, 16 unsuspected primary cancers were found for an incidence of 17%. The survival rate for 56 of these patients followed for over five years was 96.5%.(482)

***Surveillance for Other Primary Cancers*:** An association between large bowel and breast cancer has been well documented. Etiological links could be either dietary, environmental or genetic. In patients with breast cancer any gastrointestinal symptoms should alert the physician to the possibility of colon cancer. This is especially true if there is a strong family history for either cancer. Differentiation of a new primary from a solitary metastases can be difficult. Physician awareness of these possible interrelationships may improve survival for such patients.(422) Ovarian and endometrial carcinomas commonly develop in breast cancer victims.

Treatment of Breast Cancer in Males

Cancer of the male breast is a rare disease that accounts for 0.3–1.5% of all male cancers and for less than 1% of breast cancers. It reaches a peak age some five to ten years after the peak age for females, i.e. in the mid-60's.(709)

Although radical mastectomy had been heralded as the treatment of choice for male breast cancers, Robison and Montague found that more limited surgery and radiation controls the disease better and results in less disability to the arm and shoulder—an advantage that is very important for working men.

No local or regional recurrences developed in patients treated with simple mastectomy, excision, or needle biopsy and radiation therapy to the chest wall and peripheral lymphatics.

The ten-year disease free survival rate was 50% for their entire group of 39 patients, 70% for patients with a histologically or clinically negative axilla, and 34% if the axilla was positive.

Their report emphasizes that physicians should be suspicious of breast masses in males, particularly in older men. They are now studying the elective use of chemohormonal therapies for males with advanced local disease.(709)

Steinitz et al compared the 17 year incidence of male breast cancer (MBC) in Israel and the United States and found higher rates in Israel. Their series included eight of the 187 cases among Arabs. There were four families in which both husband and wife had breast cancer and one family with breast cancer in both father and son.(787)

Ramantanis et al reported on 120 male breast cancer patients in Athens, and found a 5-year survival rate of 42.9% for radical mastectomy, 40.7% for simple mastectomy and 35% for lumpectomy. There were no 5-year survivors among those treated with radiation, chemotherapy and hormonal manipulation.(687)

Metastases to Breast from Other Neoplasms

Metastases to the breast from nonmammary primary malignancies are rare. Less than 200 cases have been reported. Malignant melanoma and lung cancer (especially small cell carcinoma) are the most common sources of such cases. Gastric, prostatic, ovarian and renal carcinomas are also relatively frequent primary sites, and eight head and neck cases have been reported.(861a)

Breast involvement from extramammary cancers implies a poor prognosis. Rapid widespread dissemination occurs in 75% of patients and 80% die within a year. Recognition of a neoplasm as metastatic rather than primary in the breast is important, to prevent radical surgery and to initiate appropriate systemic therapy, including immunotherapy.

RADIATION

As Primary Treatment of Breast Cancer

Less than a year after Roentgen discovered x-rays in 1895, patients with breast cancer were receiving radiation therapy.(373) Initially, it was felt to be merely an adjunct to surgery in early cases, or a palliative in advanced cases.(33) It has now become a promising alternative to mastectomy in patients with early disease, and an effective means of local control.(684)

In 1922 Professor George Gask suggested to Sir Geoffrey Keynes that an attempt should be made to treat breast cancer with interstitial radium needles alone.(447) "For the first two years only patients with recurrent disease following operation were treated. In nearly every instance the growth was observed to disappear." The treatment was then extended to the primary disease, the first patients being treated on August 1, 1924. For the next 4½ years only very advanced or inoperable cases were so treated, and the results in 50 of these were examined before it was thought justifiable to extend the treatment to the earlier cases. It was soon apparent that the belief that cancer cells in the breast were radioresistant must be abandoned.

Some remarkable results were obtained, and by 1937 many patients had remained free from disease up to eight years after treatment.(447) Keynes reported in 1937 that a total of 325 patients had been treated and it was found that the three and five year survival rates were not significantly different from those obtained by radical surgery.(448) At this time Keynes decided to remove either the tumor or the breast *before* radiation according to circumstances. He believed that by combining radiation and conservative surgery one could achieve the best of both modalities.(447) His excellent results are described in our section on conservative surgery. (See above, pp. 49–54.)

Since 1961 Pierquin et al in France have treated over 400 cases by radical radiation therapy as primary treatment, with excellent results: 95.5% for T_1 lesions and 92.5% for T_2 lesions.(490) As to cosmetic results Pierquin et al found that 82% of patients with T_1

lesions had excellent results (no sequellae visible at first glance) or good (minimal sequelae seen on close inspection.)(671) With T_2 lesions these results were achieved in 70%. Analysis of their cosmetic results convinced Levene et al of the importance of attention to treatment details and meticulous technique in achieving good cosmesis.(490)

Other series that report comparable local-regional control include Montague et al with 96%,(582) Prosnitz et al with 93.4% for combined clinical Stages I and II,(684) and Alpert et al, with 92% for operable lesions which were largely T_1 and T_2 but included a few T_3 lesions.

The figures at the Joint Center for Radiation Therapy in Boston showed an overall local-regional control figure of 94% for combined Stages I and II.(490) They concluded that these figures can leave little doubt about the ability of primary radiation therapy to achieve local-regional control with a highly acceptable control rate in early carcinoma of the breast.(490)

Mt. Sinai Hospital in New York end results of extended vs. limited radiation techniques were reviewed to determine the amount of normal tissue that could be spared in treating women with smaller breast cancers. No significant difference in local control was found whether extended fields were used or fields limited to the breast and axilla. Accordingly they have now reduced the volume irradiated for Stage I and II breast cancer patients. Patients so treated had both better survival and remission of metastases, thus supporting the data of Vera Peters.(665;666) *Her results showed increased risk of metastatic disease as the primary treatment increased in severity*. By thus omitting direct fields in treating peripheral lymphatics they avoided possible adverse effects to the heart, lung and blood vessels.

In reducing the volume of normal tissue irradiated by using tangential fields only to treat the breast and axilla one can reduce the immunosuppressive effects of radiation and lead to lesser radiation reaction with subsequent gain in cosmesis. They devised the triple tangent technique to meet these criteria. Their detailed procedures deserve careful study. Their end results at five and ten years are excellent.(33)

A reappraisal is required of the way radiation therapy is given to breast cancer patients, so that as much as possible of the lymphoid tissue (immmune mechanism) may be left undamaged.(111) Daily doses of X-ray will destroy successive waves of populating lymphocytes before they can develop immune competence against tumor antigens.

Pierquin et al and others concluded that primary radiation therapy is a medically viable alternative to mastectomy in the treatment of breast cancer. However, certain principles must be observed in administering such therapy.

1. Moderate doses (4,500–5,000 rad) are sufficient for the control of subclinical or microscopic disease but larger doses (upward of 6,000 rad) are required for gross tumors.(684)
2. The ease with which the breast may be irradiated can be facilitated by excision of gross tumor leaving only microscopic disease to be eradicated.
3. Great attention to technical detail is essential in order to achieve excellent cosmetic results while avoiding local-regional recurrence. (Overlapping fields as a result of divergence of beams will produce subcutaneous ridges of fibrosis because of overdose: the routine use of bolus can result in undesirable telangiectasis.)
4. Local control in the breast can best be achieved by combining external beam therapy to a moderate dose with interstitial implantation or electron boost to sites of residual tumor, or to a site where there is increased likelihood of tumor being present.

Levene et al concluded that it is important to the future of such therapy that all who undertake the treatment of early breast cancer by irradiation do so with meticulous attention to these principles.(489)

***Problems*:** Radiation therapy of breast cancer is not without problems, notably the shortage of highly skilled radiotherapists. A general radiologist using antiquated equipment is *not* prepared to treat breast cancer. Vera Peters stated that first-rate equipment is being used in all Canada's provincial cancer institutes. Montague, of the Texas Medical Center, estimated a few years ago that no more than 25 to 30 radiotherapy centers in the United States were ready to treat breast cancer with the infinitely precise and delicate measures required. She added: "Even mediocre surgery is preferable to poor radiation."(582)

Not all breast cancers respond well to radiation as a primary method of treatment. The slower growing ductal tumors are sluggish, indolent growths that rarely spread to the lymph nodes or blood vessels and they are relatively radio-resistant. For these lesions surgery is ideal. Other types of infiltrating breast cancers grow so rapidly that radiation offers the only possibility of control. Still others may be equally susceptible to successful treatment by surgery or radiation. Regionally advanced cases, despite adequate local therapy demonstrate a rapidly falling survival curve, suggesting the need for early systemic chemotherapy(882) or immunotherapy.(614)

However, Holland et al observed that radiotherapy antagonizes the beneficial effect of adjuvant chemotherapy by depressing the immune response.(399)

Janssens et al noted that steroid receptor concentrations are affected by previous exposure to ionizing radiation. Therefore breast biopsy or tylectomy should be performed prior to radiation to determine steroid receptor status. Preoperative radiotherapy with 20 Gy reduces estradiol receptor concentrations by 55% and progesterone receptor concentrations by 70%. Taking into account previous radiation exposure will avoid misinterpreting the hormone dependancy of a patient's breast cancer.(426)

***Radiation with or without lumpectomy (known also as tylectomy or wedge resection)*:** A number of other authors in the past 40 years, particularly in Europe, have shown that *local control of breast cancer can be achieved by radiotherapy, either alone or following lumpectomy*. At the Fondation Curie in Paris, conservative management of breast cancer was initiated by Francois Baclesse and his colleagues in 1936. This approach has been continued there until the present time.(27)

This group reported in 1978 on 514 patients who were treated for a surgically operable (T1,T2,T3,NO,N1A,N1b) infiltrating breast carcinoma at the Fondation Curie, from 1960 to 1970 inclusive. Patients with tumors 3 cm or less and without axillary adenopathy had lumpectomy followed by radiotherapy. Patients with larger tumors and all patients with clinically significant lymph nodes (N1b) had exclusive radiotherapy. The five and ten years absolute survivals, with no evidence of disease (N.E.D.), for the lumpectomy group are 85% and 75%, respectively; 12% had secondary surgery for local recurrence. The cosmetic results were satisfactory in 98%, with no severe radiation sequelae. The five and ten years, N.E.D., of the exclusive radiotherapy group are 68% and 43%. 55% had secondary surgery for persistent or recurrent disease. The cosmetic results were satisfactory in 85%. There were only three patients with severe radiation sequelae. The overall survival for 514 patients at five and ten years are 72% and 51%. Conservative treatment preserved the breast and resulted in survival at five and ten years comparable to those of radical surgery.

Levene et al in Boston have treated 150 breast cancer patients by radiation (4,500–5,000 rad in 20 to 25 daily fractions) without mastectomy. Of these 150 cases without mastectomy, 77 had excisional biopsy of the lesion while the remainder had incisional or needle biopsy. There has been 100% local control in Stage I or II disease and 67.5%

in Stage III. Those patients who had excisional biopsy had a significantly lower incidence of recurrence than those in whom the tumor was left in situ. The cumulative survival probability at five years is 100% for Stage I, 65% for Stage II and 26% for Stage III.(367;489)

In 1979 Crile stated that if results in the centers in this country that use combinations of interstitial and external radiation prove to be as acceptable as those reported from centers in Europe and England, women will soon be able to choose between having a modified radical mastectomy and the more complicated process of relying chiefly on radiotherapy. In any event it is becoming more and more apparent that in most patients the breast can be saved without jeopardizing the chances of survival.(180)

In a series of 123 patients with primary operable carcinoma with positive internal mammary or highest axillary lymph nodes, Guttman used 2-million volt radiation and reported 52% five year survival with no lymphedema.(343)

Nobler and Venet recently reported their experience with irradiation as the primary treatment for breast cancer in 90 patients.(631) These women received comprehensive high dosage supervoltage teletherapy as the primary treatment for carcinoma of the breast following a biopsy or segmental resection and were followed 2½ to 12½ years. The tumor doses delivered to the breast ranged between 5,600 and 7,000 rad in six to nine weeks; the draining lymph nodes received tumor doses of 5,000 to 7,000 rad in six to eight weeks. Iridium-192 implants were employed to boost the radiation dose to the breast, and in seven instances a "toilette" mastectomy was performed for residual cancer. Satisfactory local control and cosmetic results were achieved in 86 of the 90 patients. The local control rates were: Stage I, 100%; Stage II, 95%; Stage III, 100%; Stage IV (M-0), 89%; Stage IV (M-1), 100%. The overall disease-free figures were: Stage I, 85%, Stage II, 48%; Stage III, 50%; Stage IV (M-0), 29%. They feel that this approach to the initial management of breast cancer is practical, useful and a successful substitute for mastectomy when medical or surgical contraindications exist or when the patient refuses mastectomy.(631)

With megavoltage radiation, the cosmetic results have been very satisfactory with minimal radiation sequelae. Mastectomy for persistent or recurrent disease has been simpler to perform with fewer postoperative complications.(119) Radiation alone can sometimes completely eradicate the primary tumor and also the secondary deposits in lymph nodes.(263) Encouraging results with local breast irradiation of small localized tumors need confirmation in controlled studies.(283;684)

By 1980 the Radiation Therapy Oncology Group, a 36 member national study group, had collected in their registry 234 patients treated with primary irradiation for Stage I and II adenocarcinoma of the breast. They reported a five-year survival rate of 83% for Stage I and 68% for Stage II. The local failure rate for T1 tumors was negligible (1.7%) regardless of whether or not complete excision of tumor was performed first. For T2 tumors the local failure rate was 9.7% if there was preirradiation excision, but increased to 29.2% if only incisional or needle biopsy was performed prior to radiation. An acceptable cosmetic result was achieved in 84% of the patients.(48)

If modern radiotherapy in expert hands is as effective as surgery in the treatment of certain breast cancers, why is it so seldom employed? Most surgeons have been trained to do a radical mastectomy. They are trained to perfect certain cherished procedures and do them well with a maximum of safety. The trouble with training, as distinct from continuing education, is that it keeps one from questioning basic procedures. Cope stated, "Now we've got to revise our thinking about breast cancer—to concentrate on improving the non-mutilating therapy and making it more generally available."(168)

Postoperative Radiation as Adjuvant Therapy

After Radical Mastectomy: The routine use of postoperative radiation following radical mastectomy is highly questionable. The poorer prognosis in such cases appears to be due to the depression of host immunological defenses in the crucial postoperative period. The immunosuppression due to such major surgery is further compounded by the immunosuppressive effects of radiation. This occurs just when carcinoma cells, released into the blood stream during the operation, are establishing themselves.(6) Within one week of beginning postoperative radiotherapy B & T lymphocytes fall to low levels. The B cell lymphopenia reverts to normal in 10 months, but the T cell lymphopenia persists for at least two to four years.(19)

Radical surgery makes radiation less effective because the vascular supply is disturbed, resulting in some hypoxia of the chest wall. Radical surgery takes four to six or more weeks to heal and radiation must be delayed until healing, or there is increased fibrosis. The solution according to some oncologists is to use less than radical surgery, i.e., (simple mastectomy or wedge resection) and postoperative radiation.(174; 528)

Arnold and Lesnick reviewed the results of *radical mastectomy* in Stage III breast carcinoma and found 33% had survived five years and 22% ten years. Pre- or postoperative radiation did not improve the survival of these patients.(23)

Simple Mastectomy, Postoperative Radiation or Watch Policy: A multicenter prospective trail of Stage I and II Breast cancer was conducted in England. By 1980 a 10 year follow up showed no significant difference in survival between patients treated by simple mastectomy alone, (with radiotherapy later if the disease recurred,) and those treated with simple mastectomy and routine immediate postoperative radiotherapy.(45) A watch policy with later radiotherapy in the approximately 25% who get local recurrences gives complete control in 70%. Many recent studies indicate that although postoperative radiation may decrease local recurrence, there is an increased mortality from distant metastases which grow more rapidly.(89; 101; 114; 145; 170; 188; 189; 276; 435; 523; 566) This study showed that after mastectomy *alone*, palpable axillary lymph nodes regressed within three months after mastectomy in 75% of patients in Clinical State II *not receiving any radiation*, (45) due to their own immune defenses.

Primary Radiation Therapy for Stage III Breast Carcinoma

These patients often present with advanced local disease that is difficult to control. Even if local control is obtained, the majority of patients develop distant metastases. Therefore, successful treatment of this stage of breast cancer must include both local and systemic therapy. Radical surgery in this setting has not been successful.(103)

At the Joint Center for Radiation Therapy at Harvard Medical School 116 patients with Stage III breast carcinoma received primary radiation therapy with a 5-year survival of 25%. In patients undergoing an excisional biopsy and an interstitial implant of the primary tumor area, local control was 100%. In contrast patients having neither an excisional biopsy nor an implant, local control was only 41%. Patients treated only with an endocrine ablative procedure following radiation had no improvement in survival or local control, but those receiving chemotherapy as the sole adjuvant or combined with an endocrine ablative procedure did have increased local control and increased survival.(103)

Radiation for Inflammatory Carcinoma of the Breast

Inflammatory carcinoma represents 1 to 4% of all breast cancers. It is often misinterpreted by patients and physicians as an infection. It carries the worst prognosis as it is *very* malignant; the tumor cells are usually undifferentiated, and the subdermal lymphatics are widely involved with carcinoma. As a result there is an acute onset of redness, pain and swelling of the breast due to lymphatic blockage and lymphangitis. The breast is hot and grossly appears to be involved with cellulitis.(841) Not only are the skin lymphatics full of tumor cells, but so are the surface veins and axillary lymph nodes on many occasions. Most of these patients die within 12 to 24 months.(117)

Conventional surgical procedures are contraindicated for this lesion.(841) They do not provide the local control of the disease observed in patients with other types of clinically localized breast carcinoma. Radiation minimizes the dangers of dissemination through surgical intervention and it provides the most effective palliation in these patients. Tumor doses in excess of 6,000 rads are recommended for control of this fulminating form of breast cancer. Chu uses twice a day fractionization.(139)

In a group of 22 patients with recurrent inflammatory breast carcinoma Chu et al used sub-total-skin-electron-beam therapy once a week to doses of 2,400 rad in six sessions. The total response rate was 91%.(625) Of the patients achieving complete response (77%), half lived six months or more and a few were alive two years after treatment with no sign of further recurrence. This technique has proved to be an effective palliative method for this rapidly progressive disease, with minimal inconvenience to the patient and drastic reduction in hospital visits.(625)

Combined Modalities for Inflammatory Carcinoma of the Breast

At M.D. Anderson a group of 32 patients with primary inflammatory breast carcinoma received chemoimmunotherapy: 5FU, adriamycin and cyclophosphamide (FAC) plus BCG followed by radiation therapy. This group was compared to 32 consecutive historical controls treated by radiation alone. The mean disease free survival for the FAC-BCG group was 16 months, compared to nine months for those receiving radiation alone. Thus the combined therapy significantly improved the disease free interval and survival of these patients.(464) We believe that the use of mixed bacterial vaccines combined with BCG to elicit the tumor necrosis factor may be more effective than BCG alone in such cases.(127)

Primary Cesiumtherapy of Breast Cancer

Between June 1960 and June 1970, 400 consecutive patients received primary telecesiumtherapy for breast carcinoma at the Cancer Institute in Marseilles.(779) Preradiation wedge resection of the tumor was performed in 160 patients. Postradiation mastectomy was performed in 92 patients because of assumed or real treatment failures. The overall 5-year survival was 69%; the breast was conserved in 80% of the survivors and 70% of the irradiated breasts remained near normal in appearance. A total of 50% of patients with residual disease in the mastectomy specimen survived. Compared to primary mastectomy, telecesiumtherapy improves the quality of survival.(779)

Radiation therapy is a far less devastating palliative than surgery in cases where the prognosis is bleak. Radiation can reach the internal mammary and supraclavicular nodes and other areas that are mostly inaccessible to surgery.

Radiation in Inoperable Breast Cancer

Inoperable breast cancer represents a considerable proportion of patients presenting with local, or local and regional disease. Vaeth et al believe that radiation therapy is the single most effective modality in bringing under control locally advanced disease.(854) It has gradually replaced radical surgery as a primary treatment for locally advanced disease in many centers, the technique most often used being a protracted course, with a dose of 4,500 to 8,000 rads delivered in 8–12 weeks. This is well tolerated and permits postirradiation conservative or even radical surgery if the lesion becomes operable.(854)

In a limited number of these patients operated upon after radiation, sterilization of the tumor was observed, but very few, if any, patients achieve cure by radiation. The delayed appearance of metastases is more apt to be due to host factors than to effective local control.

Inoperable breast cancer (T3,T4) carries a high potential for early dissemination in most patients. Therefore a successful control with local treatments such as radiation alone or radiation followed by surgery, appears of limited value in influencing the subsequent course of the disease. Since distant microscopic foci are present in a high percentage of patients coming for treatment, optimum control of the disease can only be achieved in these cases by some form of systemic therapy, i.e., chemotherapy and/or immunotherapy.

Radiation for Metastatic Breast Cancer

Breast cancer may spread by direct extension, by lymphatics or by blood stream or by all three. Blood stream spread leads to involvement of the skeleton and remote viscera. The former is often compatible with long life, the latter (to liver, brain or lungs) is often rapidly lethal. Poor liver function may reduce estrogen inactivation and worsen the disease. Frequently metastasis to the site of production of stimulating hormones (ovaries and adrenal and pituitary glands) is a striking and significant finding.(428)

The use of radiation therapy in the initial management of bone metastases in breast cancer patients is usually effective in relieving pain and improving performance status. Radiation for visceral metastases is often palliative.

Deleterious Effects of Radiation

The early and late deleterious effects which may occur after radiation therapy of breast cancer include the following: Leukopenia, lymphedema, damage to liver, lung and heart tissues, rib fractures, neuropathy (brachial plexus), fibrosis, osteogenic sarcoma or fibrosarcoma or lymphangiosarcoma, and acute leukemia.

These complications following irradiation for breast cancer have led radio-therapists to avoid the higher dosages formerly used.

Leukopenia: The effect of postoperative radiation on the total white blood count has been reported as markedly decreased in 75% of patients receiving chest wall and nodal irradiation, and in 50% of patients receiving only peripheral nodal irradiation.(493)

The lymphopenia lasts for at least a year and is mainly selective for T cells.(799) It lasts 60 months in some cases.(523; 566) Local immunity measured by the ability to react with a delayed hypersensitivity reaction may be decreased within the irradiated area.(796) These findings may be relevant to the development of distant metastases.

In a study of the immunological effects of treatment in locally advanced breast cancer the percentage and absolute T-lymphocyte (E-rosette) count, absolute lymphocyte count and T-lymphocyte blocking effect of serum was sequentially quantitated in 33 Stage III breast cancer patients and to age-matched controls. There was significant and prolonged depression of T-cell counts in the group treated by radiotherapy and this correlated with increase in the T-lymphocyte blocking effect of serum. In contrast, removal of the tumor in the mastectomy group was followed by increased T-cell counts and the T-lymphocyte blocking factor of serum disappeared. Papain treatment returned the low T-cell percentage counts to normal levels in both groups.

The results show that radiotherapy has a dual effect on T-lymphocytes. The first is a direct lethal effect on all lymphocyte subpopulations which results in a diminished absolute T-lymphocyte count. The second effect is through the enhanced release—above that seen before treatment—of an E-rosette receptor masking factor. This may be a cellular by-product of radiation-induced tissue damage. The effects of the second mechanism, but not of the first, are reversible by the proteolytic action of papain.

The E-rosette receptor masking factor in the serum of breast cancer patients disappears following mastectomy, showing that it is a tumor related, though not necessarily tumor specific factor.(749)

Wallgreen et al strongly argue against the thesis that radiotherapy-induced lymphopenia promotes the development of metastases in breast cancer patients. They believe that radiotherapy should not be withheld on immunological grounds since they believe there is no proof that temporary depression of lymphocyte function or moderate T-cell lymphopenia is hazardous for patients with breast cancer. This group found that a dose of 4,500 rad over five weeks prior to surgery reduced the incidence of local and regional recurrence and of distant metastases, as compared to the surgery only group (modified radical mastectomy). Surgery in the radiation group was performed six weeks after completed radiotherapy.(867)

We do not believe that any study has been made to compare the degree of lymphopenia produced in Japanese or Finnish women following conservative surgery and postoperative radiation, with that seen in women in England or the United States. Perhaps the better prognosis observed in the Japanese and Finnish women is due to the host-stimulating effects of their very hot baths and sauna—these may prevent or lessen lymphopenia. Intraductal carcinoma in Japanese women more often forms a mass in which there is a prominent lymphoid reaction.(714) Stjernwärd stated: "With the need for both therapeutic and economic priorities in medicine, we should be more critical in recommending post-operative radiotherapy in early breast cancer. It demands the physician's time, the patient's time and scarce resources, yet it may, we assert, be associated with increased early mortality, an iatrogenic failure."(797)

Lymphedema: Marked lymphedema develops in a much larger percentage of breast cancer patients who receive radiation after radical mastectomies than in those managed by surgery alone. The swollen arm is still the greatest long range complication following radical mastectomy.(723) (See above page 44.)

Late Deleterious Effects

Liver: Hoffman reported that the danger of radiation damage to liver tissue in breast cancer patients is not well appreciated. Radiation dose tolerances for liver tissues are

generally felt to be 3,000 rads delivered over a period of three to four weeks. He urged that it is important to recognize the possibility of radiation induced liver disease and even radiation hepatitis in patients given radiation to the chest wall. Since breast cancer has a high predilection for hepatic infiltration, recognizing the difference between radiation damage and metastases may alter further therapy. Since many cytotoxic agents are cleared and metabolized by the liver, adding chemical therapy to an already ailing liver may be hazardous.(394)

***Rib Fractures and Cardiac or Pulmonary Reactions*:** Harris et al reported rib fractures in eight patients and pulmonary reactions in another five.(366) Many authors have reported on cardiac complications after irradiation for breast cancer. Stewart and Fajardo found these occurred in 4.5% of their patients due to radiation induced fibrosis.(793) Nivet et al reviewed the literature on these cardiac complications including precocious myocarditis or myocardial infarction, fibrosis or stenosis of the coronary arteries.(630) Pulmonary fibrosis can also be a serious problem.(718)

***Radiation Induced Neuropathy*:** Also serious is radiation induced neuropathy.(718) Brachial plexus exploration in difficult diagnostic situations will permit early treatment and avoid debilitating loss of function. However, treatment of radiation neuropathy has remained largely ineffective.(28) Perhaps in future, such cases should be given injections of mixed bacterial vaccines, which have proven of great value in complete control of pain syndromes of diverse origin.(602–619)

***Fibrosis*:** The long protracted technique, initiated by Baclesse in the 30's (27) was used between 1970 and 1972 at M.D. Anderson Hospital in Houston, Texas. It was chosen because it was the only one that had produced a significant percentage of control in larger lesions, and because it avoids moist desquamation. Analysis of 158 patients so treated in this period showed that all patients had some fibrosis. Complications continued to appear at an undiminished rate in patients surviving more than 10 years, increasing for doses over 8,100 rad. Although high dose protracted radiation is no longer used for breast cancer, these data proved a warning that late complications may occur many years after treatment in patients who had large volumes irradiated.(27)

***Carcinogenic or Leukemogenic Effects*:** Sarcoma of the chest wall may develop following postoperative radiation therapy, even as little as 2,500 rads. At least 25 such cases have so far been reported.(846) Among these, fibrosarcoma and osteogenic sarcoma were most frequently encountered. A cutaneous angiosarcoma developed in a mastectomy scar four years after postoperative radiation.(354)

A case of multicentric breast cancer was reported that developed 10 years after irradiation for lymphoma involving the breast.(504)

Acute paramyeloblastic leukemia developed in a woman doctor who had received surgery and radiation therapy for a carcinoma of the left breast (8,400 rads.) She also received radiation to the ovaries to produce menopause (4,800 rads) causing leukopenia requiring transfusion. Within 13 months after completing this treatment she developed acute paramyeloblastic leukemia which caused death nine months later.(931)

Rosner et al made the most comprehensive report on breast cancer patients who developed acute leukemia, including 24 patients of their own and 54 in a review of the literature. In addition they observed 3 cases of chronic myelocytic leukemia and found

13 others in the literature. The mean interval between the diagnosis of breast cancer and the onset of leukemia was 6.9 years.

Seven patients received no postoperative radiation or chemotherapy, and the development of leukemia 1 to 23 years later could not be attributed to therapy for breast cancer. Forty-one received radiation after mastectomy. Combination radiation and chemotherapy was given to five and chemotherapy alone to three other patients. *The incidence of acute leukemia in breast cancer patients is seven times as frequent as the expected incidence.*(717)

Lymphangiosarcoma: This tumor develops in the swollen arm following irradiation and radical mastectomy.(See above page 46.)

Cosmetic Problems: Local excision and radiation are less mutilating than mastectomy, and almost always produce superior cosmetic results. However, in a few cases breast preservation may result in a cosmetic catastrophe. Finally, the possible long range carcinogenic effects of high-dose radiation, which may appear up to 20 years later, must be considered.

Photoradiation Therapy

Photodynamic processes have been known since 1900, and the ability of certain photodynamic agents (especially porphyrins) to accumulate in malignant tissue has been recognised for more than 30 years. They were used originally to help *detect* cancer. However, until Dougherty et al began their studies at Roswell Park about 1972, there has been little published data relating to the use of in vivo photodynamic methods to *treat* cancer.

By 1981 Dougherty had treated 35 metastatic breast cancer patients. Their lesions ranged from a single large one 12×12 cm to multiple metastases over areas involving from 10 cm^2 to the entire anterior and posterior chest wall. In this group responses occurred in 34 of the 35 patients, (at least 50% reduction in size or extension of disease.) However, only 16 of these cases survived over six weeks after treatment and 10 of them showed recurrences in the treated area, apparent two to nine months post-treatment. Only six had not recurred up to a year after treatment.

Photoradiation therapy for breast cancer is still in an early stage of development. It can be used as a primary treatment or for recurrent breast cancer following conventional modalities such as surgery, radiation or chemotherapy. The therapeutic ratio depends upon the relative drug levels in tumor and surrounding normal tissues exposed to similar doses of light. While many normal tissues clear the hematoporphyrin derivative (Hpd) more rapidly than do the tumors, the skin retains it for up to 30 days after injection. Therefore patients receiving such therapy must avoid direct exposure to sunlight for a month.

Contributing factors to the development of skin necrosis appear to be multiple doses given in less than two months, especially in obese patients, ulceration of the area under treatment since Hpd is also taken up by traumatized tissue, prior adriamycin plus ionizing radiation in the PRT field, and inflammatory carcinoma. While in these cases adequate healing has always occurred, large eschars are quite painful and may require one or two months to heal.(224)

We believe that it may prove beneficial in these patients to administer Vitamins A and C and mixed bacterial vaccines to lessen pain and help stimulate the reticuloendothelial

system to clear the skin and to hasten healing. (See below, Parts II and III for the effects of bacterial infections or vaccines on healing and regeneration of normal tissues.)

CHEMOTHERAPY

Introduction

Dr. Lewis Thomas in a review of Lucien Israel's book, *Conquering Cancer*, stated "The skeptics and critics of chemotherapy question the value of *limited* benefits in diseases like cancer. How much is it worth, or is it worth anything to be able to live six months longer, with a disease that will surely be fatal at the end of that time. What about one year? Three years? Five years? Ten?

"This is the sort of question being asked these days of many cancer patients and their families. It is, thanks to refinements in technology, no longer complicated by other harsher terms: very few patients are incapacitated by chemotherapy contrary to the popular impression. They are not "poisoned"; beyond a few hours of nausea, vomiting and transient weakness, they are not made to feel sick; some of them lose scalp hair but only temporarily, and wigs serve adequately while the new hair grows back in, as it always does. Almost all of them are far more comfortable and free from pain than they would be without treatment. So it is really a question of time. Is it possible to live well under the nonetheless certain and predictable prospect of dying? One answer is, of course, that this is what life is like for all of us. We are all sure of dying, but most of us are not obliged to accept this and are allowed to believe that we'll go on forever.

"Another answer comes from many of the patients undergoing this kind of treatment, and there is no question about their feeling. They want very much to be treated. They feel better for it, they can usually return to the activity of their former lives, and *most important of all they receive hope*. . . . There is the hope of being one of the . . . small number of permanent cures. And there is the hope that in a field of clinical science moving as rapidly and surprisingly as this one, something new and decisively effective may turn up next year."

Mechanisms of Action

Neoplasia is often associated with a disturbance between the immune processes of facilitation and rejection in favor of tumor enhancement. The various chemotherapeutic agents exert their direct cytotoxic effects on proliferating cancer cells at different stages in the cell cycle and on different parts of the cell. This is the rationale for using combined regimens. In addition to these effects chemotherapy may exert a differential effect on these immune processes, reversing the imbalance in favor of tumor rejection. The current position seems to be that chemotherapy selectively depresses the non-thymus-dependent or B-cell portion of our immune defenses, but may allow an increase in the T cell defenses to occur. Animal experiments suggest that when combined chemo-immunotherapy is used, the timing of the two components is crucial to the effect achieved on the immune system, and therefore on the tumor.(592)

Looney et al noted that dosage and frequency of administration of adriamycin, cyclophosphamide and 5-FU are of great importance. A significant reduction in life occurred after five fractionated doses of 5-FU, but not after a large single dose. The increase in mortality is attributed to prolongation of the onset of recovery of bone marrow. Large

intermittent single doses of chemotherapeutic agents given following recovery of the host from a previous treatment is less toxic to the host and equally effective in control of tumor growth.(511)

Side Effects

This is an age of rapidly advancing chemotherapy and multimodality therapy holding promise of greater palliation and in some cases possible cure. However, we believe that many oncologists have not fully recognized that this therapy may be associated with potentially life-threatening side effects and should not be administered to patients without their full knowledge and consent. Patients should be informed of the circumstances necessitating such therapy and these side effects so that together with the oncologist and the supporting staff they make an informed decision.(361) Open communication is reassuring and decreases stress and anxiety which in turn affect the body's ability to respond to chemotherapy effectively.

The object of chemotherapy is to do the maximum damage to the tumor with the minimum damage to the patient. Price, Hill and Ghilchik in their new book, *Safer Cancer Chemotherapy*, outline how this can best be accomplished.(682) Oncologists treating breast cancer by chemotherapy should read this excellent monograph, especially chapters 4, 5 and 6, which deal with its use in both early and advanced breast cancer. They have shown that today "chemotherapy can be administered much more safely than at any time in the past without loss of therapeutic effect. The advantages of this approach for patients with advanced disease are considerable; namely a) they spend only one night every three or four weeks in hospital; b) there is no serious damage to bone marrow provided certain precautions are vigorously observed, so there is no need for intensive supportive care such as platelet transfusions and antibiotics, etc.; c) the number of visits to the hospital is significantly reduced; d) there is no loss of therapeutic effect; e) even intensive chemotherapy can be offered, and may produce a significant increase in the cure rate of certain common neoplasms such as breast cancer, by giving chemotherapy as part of the initial attack, combining with surgery and/or radiation.

"All the experimental and clinical studies to date clearly indicates that in order to increase the cure rates chemotherapy has to be given very intensively. Many surgeons and radiotherapists in the past have objected to this on the grounds of unacceptable toxicity. However, now that it has been shown that such toxicity can very largely be avoided, an improvement in the cure rates is now easily within our grasp, provided that more clinicians use this approach." (Personal communication from L. A. Price, 9/29/81.)

***Nausea and Vomiting*:** These are among the most common and distressing problems the physician is called upon to resolve in the breast cancer patient undergoing chemotherapy or radiation therapy. If left unchecked, they result in depressed nutritional state, serious metabolic derangements, deterioration of the patient's mental and physical condition and possible rejection of potentially useful treatment of the cancer. Thus, control of these symptoms is essential for the patient's well being and survival. Control by classic antiemetics has been incomplete and variable.(301;328;380;727a)

Antiemetics: According to Frytak and Moertel at the Mayo Clinic, the phenothiazines are really the only marketed drugs with well-established effectiveness.(301) Chlorpromazine has decided cost advantage but has not been frequently used as an antiemetic in recent years because it produces toxic hepatitis more frequently than other phenothiazines.

Prochlorperazine has been the most widely studied and probably enjoys the most common clinical use. Preferably it is given orally in tablets if clinical circumstances permit (in doses of 5 or 10 mg. three times daily.) It is not necessary to use the more expensive sustained release spansule. If patients cannot reliably tolerate oral medication, an intramuscular injection of 10 mg. or a rectal suppository of 25 mg. can be used. If this agent is not effective there would seem to be no rational basis for switching to another phenothiazine.

Haloperidol, though not well studied may offer a therapeutic alternative of an oral dose of 1 mg. three times daily. Antihistamines, barbiturates, trimethobenzamide, hydrocloride and benzquinamide do not seem to have sufficient therapeutic potential to warrant consideration.(301)

Herman et al found that nabilone (N), a new synthetic cannaboid, was more effective in controlling nausea than prochlorperazine (P): 80% of the patients responded to N vs. 32% to P. (380)

Sallan compared the effect of Delta-9-tetrahydrocannabinol (THC), the active ingredient of marijuana, with placebos in a double blind crossover trial with patients who had failed to benefit from standard antiemetic therapy. They found there were more complete responses to THC courses than to Compazine. Younger patients (under 20) had a higher proportion of complete responses than older patients. THC also proved to stimulate appetite and food consumption.(727a)

Recent randomized trials at Memorial Sloan-Kettering Cancer Center indicates the antiemetic efficacy of high dose metoclopramide in patients receiving cisplatin. In the first trial patients were randomly assigned to receive either metaclopramide or placebo. In the second they received either metoclopramide or prochlorperazine. Patients receiving metoclopramide had significantly fewer episodes of emesis than patients receiving placebo or prochlorperazine. It was also more effective in shortening the duration of emesis. Side effect were minor, with mild sedation frequently observed.(328)

Alopecia (Loss of Hair): A particularly distressing side effect of many drugs is loss of hair leading to baldness requiring a wig.(737) The oncology team should include a psychiatric social worker who can help alleviate the anxiety and stress this engenders. Sources of wigs and how to wear scarves and assurance that the hair will grow out all help. (In New York City the American Cancer Society provides wigs to women who cannot afford to buy them.)

Cooling the scalp to 25°C. or less can reduce and sometimes prevent hair loss. Several cooling systems have been devised including the ice turban, in which plastic bags containing crushed ice are bandaged to the head; gel packs, a number of which can be molded to a wig stand, strapped together, frozen and then applied to the scalp;(17) and cool caps which use the cooling generated by mixing ammonium nitrate and water within the cap. All these have been reported to be effective, but all have disadvantages: The ice turban and gel packs are heavy, cumbersome and messy and take up nursing time, whereas the cool cap has a very limited cooling capacity. All these systems warm up after application so the amount and duration of cooling are unpredictable. Because of these limitations no system has come into wide use, and as cancer chemotherapy increases, more patients are having to wear wigs due to alopecia.

Guy et al recently devised a simple system which uses a thermocirculator to pump coolant between two layers of a light-weight plastic cap. This system overcomes the disadvantages of the others and allows precise temperature control.(344) (Write Dr. Duncan Geddes, The London Chest Hospital, London E2 9JX for details.)

***Venous Thrombosis*:** Another side effect which may occur as a result of adjuvant chemotherapy for breast cancer is venous thrombosis. In a prospective randomized study of three different postmastectomy chemotherapeutic regimens (all of which used cyclophosphamide, methotrexate and fluorouracil) it was found that 5% of 433 patients had venous thromboses, and two episodes were fatal. Postmenopausal patients were at higher risk.(90)

This complication might be avoided if an anticoagulant was used in conjunction with chemotherapy.(828–834) No patient receiving injections of mixed bacterial vaccines for cancer is known to have developed thrombosis.(291–295;571;606–619)

***Cardiac Toxicity*:** Other serious side effects may occur with adriamycin which causes dose related cardiac toxicity. This exposes patients to severe and even fatal cardiac impairment decompensation. There is a great variation from patient to patient in how much of this drug can be tolerated. Vitamin E pre-treatment decreases cardiotoxicity and cell membrane lipid peroxidation in adriamycin treated leukemic mice, but may cause potentiation of bone marrow to the drug.(7) Until more direct means are established to prevent adriamycin induced congestive heart failure, it is suggested that the total dose of adriamycin should be limited to less than 500 mg. per meter square to permit safer use.(479)

***Lymphopenia*:** Adjuvant cyclic chemotherapy for breast cancer induces lymphopenia and impairs certain lymphocyte function as measured *in vitro*. Despite this drug induced immunosuppression Strender et al believed that these patients do not become more susceptible to infections.(810)

***Carcinogenic or Leukemogenic Effects Due to Immunosuppression*:** Since many of the chemotherapeutic agents have carcinogenic or leukemogenic potential, one must expect to find that a certain number of breast cancer patients who receive prolonged chemotherapy for metastatic disease may ultimately develop leukemia or a second primary as a result of this long term treatment.(191;364;407) This has occurred in a number of breast cancer patients.(191;397;439;442) Methotrexate does not seem to produce immunosuppression, when given in pulse doses with citrovorum rescue at infrequent intervals.(219) The high dose methotrexate regimen is effective where the usual low doses have failed because of the ability of high doses of this drug to saturate the tumor cells by passive diffusion.(220)

It is only an accident of priorities that many drugs were first known as anti-cancer agents rather than as immunosuppressants. Six types of chemicals are the stock in trade of cancer chemotherapists: alkylating agents, purine analogs, folic acid antagonists, halogenated pyrimidines, the vinca alkaloids and the corticosteriods. Each of them very significantly depresses the immune system. Each can completely inhibit the synthesis of circulating antibodies. Pre-existing immunity can also be impaired, but, in general only with large doses. These agents also depress cellular immune responses (delayed hypersensitivity.) Not all compounds with anti-tumor activity are immunosuppressive. It seems paradoxical to treat cancer with drugs which inhibit the very system considered essential for protection against neoplastic cells.(741)

The demonstration that immunologically related lympho-reticuloendothelial (L-RE) responses influence the survival of breast cancer patients should be considered in regard to therapeutic modalities which alter immunocompetence. The use of adjuvant chemo-

therapy for patients with well-defined L-RE responses to their breast cancers might do more harm than good.(63)

***Possible Detoxifying Agents*:** Further studies are required to determine which vitamin and mineral supplements may protect the cancer patient during chemotherapy without decreasing the effectiveness of the agents used. Iron supplements must *not* be given. This is discussed in the section on nutrition.(204)

Vitamin C is believed to potentiate the tumor destructive effect of a number of chemotherapeutic agents in common use, with the exception of methotrexate, whose effects may be reduced.(120, Chapter 6) It has been suggested that high doses of Vitamin C (Sodium ascorbate or ascorbic acid) protect patients against the unpleasant side effects of chemotherapy. However, Cameron and Pauling proposed that it may be wise *not* to take Vitamin C during each treatment cycle to allow the drug its full action, but to take it between courses to restore the depletion caused by the illness and accentuated by the chemotherapy.(120)

***Psychiatric Morbidity*:** Significant psychiatric morbidity, a year after mastectomy, appears to be more common in patients receiving adjuvant chemotherapy than in those receiving radiation. Only long-term cooperative studies can provide firm answers as to whether the additional social and emotional costs associated with adjuvant chemotherapy are justified by significant disease-free survival, or whether chemotherapy should be reserved for those who develop metastases.

McCardle et al believe that further studies are required to assess the emotional implications of cytotoxic therapy for the patient, her husband and family before adjuvant chemotherapy should be routinely adopted for breast cancer patients.(516a)

As an Adjuvant to Surgery

Chemotherapy as an adjuvant to surgery for Stage II breast cancer has been used by many clinicians in the past few years, especially for patients with positive lymph nodes. Preliminary results indicated a significant decrease in recurrence rates in premenopausal women receiving such therapy.(84–87;899) Prophylaxis of distant metastases in primary breast cancer should be regarded both as *prevention* of secondary tumor foci which might develop from tumor cells circulating in the blood and lymph, and as *treatment* of latent metastases in distant organs which were not apparent prior to surgery. It has been suggested that such chemotherapy should be started very soon after mastectomy and continued in three to four courses at six to eight week intervals.(450)

By far the most impressive results of such treatment have come from Holland and his group at Mt. Sinai Hospital with their report of a 68% eight year survival in patients with breast cancer with four or more involved nodes. Their five drug protocol caused no deaths, and there were only two infectious complications from 650 treatment courses and only two subsequent neoplasms, one of the contralateral breast and one of the ovary.(167)

Bonadonna's group in Milan have used cyclophosphamide, methotrexate and 5-Fu (CMF) in a large series of cases, and at first reported that the advantage of giving 12 cycles of postoperative CMF was limited to premenopausal women.(85;88) This observation is apparently in line with that of Fisher after either thiotepa or melphalan.(277) Later studies suggested there is benefit to postmenopausal women, provided they received the prescribed dosage and duration of therapy. Bonadonna et al retrospectively analyzed

the role of the dose level of CMF in postoperative adjuvant chemotherapy for breast cancer and for metastatic breast cancer.(86)

Vorherr (1978,9182) analyzed Bonadonna's Milan study and noted that the data on five-year survival fall short of expectations, the benefit from adjuvant chemotherapy being only 4% in the premenopausal women.(863) In recurrent disease, responders to chemotherapy have an average duration of remission of 15 months. Eventually the recurrence rates of treated and untreated patients become similar. If adjuvant chemotherapy weakens host defense, survival may be shortened. *Postmenopausal patients had a 5% decrease in five-year survival as compared to the controls.*(862) Vorherr added that since only proliferating tumor cells respond to cytotoxic drugs, arbitrary selection of the first year after mastectomy for adjuvant chemotherapy will only benefit 15–25% of the patients, since the other 75–85% will be treated at a time of tumor cell dormancy (mitotic rest) when chemotherapy is not effective. In view of the drastic interference with the quality of life and the limited benefits *it seem best to focus on early diagnosis of recurrent disease for immediate use of chemotherapy or endocrine therapy.(862)*

Baum in criticizing Bonadonna's trial, also noted that the benefit in overall survival at five years was only 4% in premenopausal women, whereas in the postmenopausal group the controls appear to have a slight advantage over the patients treated with CMF.(42)

Vorherr noted that 83% of their patients could not tolerate a "full or nearly full dose." He added that the hazards of polychemotherapy are substantial. Mortality may be as high as 4.4%. Side effects (which we have described above) are common and the patients feel ill. Palmer et al discontinued their trial of adjuvant chemotherapy because of severe, partly "unbearable" side effects.(647) Vorherr concluded that in view of the many uncertainties and controversies about adjuvant chemotherapy, which itself has serious health hazards, no breast cancer patient should routinely be subjected to it.(863)

Despite these criticisms, by 1981 Bonadonna concluded that their results were related to the level of drug administered as well as to the number of axillary nodes, but not to menopausal or estrogen receptor status. He added that future analyses will better define the optimal duration of CMF chemotherapy (12 vs. 6 cycles) as well as the efficacy of sequential non cross-resistant regimens.(84)

In 1982 Bonadonna reported that the most interesting recent finding which emerged from updating their results was the fact that freedom from relapse and survival were not significantly different between patients who received six cycles and those who received 12 cycles. The nadir in surviving tumor cells is probably reached in the majority of cases in less than six cycles. Their data indicated that the main important pharmacological factor is the peak level of the drugs and not their total amount over a long period. Therefore the therapeutic usefulness of prolonged treatment with the same cytotoxic drugs must be critically re-evaluated.(88)

Although in Sprague-Dawley rats given three different doses of CMF, a strong dose-related carcinogenic effect was noted by Hals and Schmal (in press), Bonadonna's group have failed to detect an increased incidence of second primaries in their five-year analysis.(88)

Buzdar et al recently reported on the five year results of adjuvant therapy with 5-FU, doxorubicin (adriamycin) and cyclophosphamide (FAC).(115) All patients also received nonspecific immunotherapy with BCG. Aggressive treatment with FAC significantly improved survival of high risk patients (Stage II and III breast cancer.) Effectiveness was not dependent on menopausal status. Higher doses were used than in most other adjuvant studies. Adriamycin was included and this is one of the most active agents in the treatment of breast cancer. Chemotherapy was ineffective in patients given postoperative radiation. A small number of patients receiving reduced doses had inferior disease free survival.(115)

For Occult Disseminated Disease

Evidence is firm that a large number of patients with primary breast cancer undergoing surgery with intent to cure, already have occult disseminated disease. Consequently the removal of the primary tumor, by whatever operation, must be regarded as inadequate therapy. Systemic adjuvant therapy offers hope of improving the survival of such patients. This can consist of endocrine therapy (tamoxifen), chemotherapy or immunotherapy alone or combined. Tamoxifen and immunotherapy are discussed later.

For Advanced or Recurrent Disease

Salmon and Jones reported the use of adriamycin and cyclophosphamide alone or with other agents, and stated that they had clearly provided excellent palliation and improved survival in patients with advanced or recurrent breast cancer. They believed this regimen should be used as initial cytotoxic therapy: the brief intensive program as a surgical adjuvant shows considerable promise for eradication of occult micrometastases in both pre- and postmenopausal women.(728)

At Dana Farber Cancer Center, Henderson et al reported prolonged disease-free survival in advanced breast cancer treated by the combination "super CMF" adriamycin. The total response rate and the complete remission rate are substantial and the durability of the responses appears to be considerably greater than that obtained with other drug combinations.(377)

Patients at Higher Risk

Holland's group at Mt. Sinai Hospital treated 100 women with primary breast cancer having four or more metastatic axillary nodes for nine months postoperatively with vincristine, cyclophosphamide, methotrexate and fluorouracil (VPCMF). For 73 women so treated, observed for 5½ years, median disease-free status was 68% at eight years. No significant difference was found between the response of pre- and postmenopausal women in disease-free survival. Mortality compared to expectation was sharply reduced: only nine of 73 had died by 1979. These results demonstrate the long-term effectiveness of relatively short term surgical adjuvant combination chemotherapy in cases at high risk.(167)

Considering the number of primarily inoperable cases, as well as the number of recurrences which develop beyond the usual five year observation period, cure rates for breast cancer remain at about 30%. Thus 70% of all these patients will sooner or later require a systemic form of treatment for metastatic disease. Combined cytostatic drug therapy or high dose methotrexate with citrovorum factor rescue may be effective in the prognostically worse forms of metastatic breast cancer.

However, Powles et al recently stated that overall survival of patients with primary breast cancer has not improved in the past ten years, despite increasing use of multiple-drug chemotherapy for treatment of metastases. Furthermore, there has been no improvement in survival from first metastasis, and *survival may even have been shortened in some patients given chemotherapy*. Chemotherapy probably does prolong survival in some patients, and further studies should be undertaken to identify these patients in advance.(676)

Chemotherapy for Inoperable and/or Metastatic Breast Cancer

Since Greenspan's report in 1966 of an effective multiple drug chemotherapy regimen for these cases, there have been many protocols devised for such therapy. Greenspan

stated in 1966 that combination chemotherapy programs then in use, in spite of using five or six agents at a time, had not significantly improved the response rate and duration of remission and survival in patients with metastatic breast cancer.(334)

Another factor to consider is that after failure or relapse of the disease when all active drugs have been exhausted, further management is compromised and is limited to less effective or investigational drugs.

The Mayo Clinic group noted that objective regression rates were 59% without vincristine, and 46% with vincristine, the other agents being 5-FU, cyclophosphamide and prednisone. Decreasing response rates were noted as the length of time increased after menopause. Since vincristine decreased the response rates and increased toxicity, its continued use in such cases seems unwarranted.

Others have used low dose CMF for treatment of poor risk patients, and have achieved regression rates similar to the higher dose protocols with minimal toxicity.(172)

At M. D. Anderson Hospital in Houston, Legha et al obtained complete remissions in 116 metastatic breast cancer treated with combination drug therapy. The median duration of complete remission was 17 months. Disease recurred in 70% of these patients from 3 to 44 months after complete remission occurred. The duration of remission was inversely related to the bulk of metastatic tumor. The short duration of complete remissions and tendency to relapse in sites of initial involvement suggest that these patients still had substantial residual tumor.(480)

We believe that if such patients were given immunotherapy (MBV) combined with chemotherapy, more prolonged or permanent results might be achieved.

Decker et al reported on 438 cases of metastatic breast cancer in nine randomized trials. Only 11% of these patients had complete regressions while 89% had partial regressions. *All but one of those who regressed had relapses.*(194)

A Swedish group reported on results in 50 cases of metastatic breast cancer treated by combined vincristine, adriamycin, cyclophosphamide and methotrexate with citrovorum factor rescue. *They found this regimen was well tolerated and 78% of the patients achieved objective fairly long remissions with improvement in quality of life regardless of the sites of the metastases.* The median duration or remission was 11+–15+ months about the same as in other reported series, but the result in skeletal metastases (75%) was better, as well as the rate of response when used as a second line treatment. One reason for this is the prolonged duration of therapy, since the objective response of the skeleton was mostly not observed until after several courses of chemotherapy. Earlier investigators probably stopped treatment too soon, hence did not observe regression of bone metastases.(554)

Extensive trials of combinations that include adriamycin are under way.(404) As stated above, this agent causes congestive heart failure, usually reversible,(431) but it is considered one of the most effective single agents in the treatment of metastatic breast cancer, and produces a tumor response rate of 28 to 55% complete or partial remission.(404;445;621) The median duration of response in one study was ten months.

In Israel, Rizel et al reported on first, second and third line chemotherapy programs in metastatic breast cancer and concluded that sequential administration of such regimens offers the opportunity for repeated remission in patients with active metastatic breast carcinoma and results in prolonged survival of responders. However, they noted that six of their patients developed fatal septic shock while leukopenic on CMFVP.(700)

Abeloff and Ettinger at Johns Hopkins reported on 34 patients with metastatic breast cancer treated by adriamycin-cyclophosphamide induction followed by alternating combination therapy.(1) They achieved an objective response rate of 56%. Their results support

those of other investigators that combination chemotherapy seems to have reached a plateau in its capacity to control metastatic breast cancer, and that alternating regimens do not appear to increase the length of remissions. The availability of new agents and the utilization of immunotherapy may result in more effective treatment programs for advanced breast cancer.(1)

Importance of Sequence of Combination Chemotherapy

Oncologists are becoming increasingly aware of the importance of these factors. The use of some agents initially may prevent the response of others given subsequently. For example, cytoxan, 5-FU and prednisone-treated patients, whether responders or failures, uniformly failed to respond to subsequent adriamycin.(621)

Of the many drugs used in treating breast cancer, methotrexate (MTX) and 5-fluorouracil (5-FU) are among the most commonly used. Recent in vitro and animal tumor studies suggest that *sequential MTX and 5-FU may be more tumoricidal than either drug used alone or in conventional combinations*.(316) Gewirtz and Cadman noted that the greatest number of responses occurred in skin and soft tissue metastases. Disease-free interval, hormonal status and prior therapy with the exception of drug regimens containing MTX and 5-FU, did not appear to affect response rates. Toxicity was minimal. They believed larger trials are warranted.(316)

The Roswell Park group has tried to avoid premature exhaustion of therapeutic modalities and has developed optimal sequential combination therapy.(716) They concluded from their experience that the first choice for chemotherapy in estrogen-negative tumors or in patients with positive estrogen and prior hormonal manipulations should be a two or three drug regimen (cyclophosphamide, 5-fluorouracil + or − prednisone,) because of their effectiveness and relatively low toxicity after failure or relapse, methotrexate and vincristine should then be added as a valuable, effective secondary program. The cyclophosphamide-adriamycin combination may then be used as a tertiary regimen. Such a stratagem provides the opportunity for further responses and prolongs survival.(716) Several investigators have observed good regression rates with high dose combinations of cyclophosphamide, methotrexate and 5-FU.

Effect of pH on Response to Chemotherapy

Meyer recently suggested that tumor energy metabolism might be restricted by low pH levels, and that tumor cells might thus be made more susceptible to systemic chemotherapy. His experimental results lend tentative support to this hypothesis.(562) We believe that bacterial infections, inflammatory episodes and injections of bacterial vaccines in or near a tumor cell induce a lower pH. This may be one of many mechanisms whereby they produce necrosis and regression of tumor.

Combination Chemo-immunotherapy

The addition of immunotherapy with BCG to a three drug combination of 5-FU, adriamycin and cyclophosphamide (FAC) resulted in a significant prolongation of remission duration and survival.(341) This regime has been evaluated at M.D. Anderson Hospital for over three years as an adjuvant in Stage II and III breast cancer patients with positive axillary nodes. In this group the estimated proportion remaining disease-free at

two years was 91%, as compared to 69% in a group of historical controls who received no adjuvant therapy.(341)

Cohen et al in Chicago reported no significant difference with respect to recurrence rate in patients receiving chemotherapy (CFP) following radical or modified radical mastectomy for Stage II and III breast carcinoma and those receiving CFP plus BCG.(142)

Chemo-Radiotherapy versus Chemo-Surgery

Bonadonna's group in Milan reported on a prospective randomized study of two combined modality approaches: chemotherapy plus radiotherapy or chemotherapy plus mastectomy.(197) They used adriamycin plus vincristine for three cycles before either local-regional modality, and subsequently gave seven more cycles. Although a higher proportion of women achieved complete remission after mastectomy (100%) compared to those given radiotherapy (60%), the total response at the end of treatment was identical (75%).

See below Part III for the end results in breast cancer patients who had *not* received immunosuppressive therapies prior to immunotherapy.

Chemo-endocrine Therapy

Legha et al reported on a series of 136 patients with metastatic breast cancer who received adequate trials of hormonal therapy and who were evaluated to determine the relationship of response to prior hormonal therapy and the results achieved with subsequent combination chemotherapy.(480) Fifty-three patients had shown objective responses and 83 had failed to respond to the commonly used modes of endocrine therapy. Of the 53 hormone responsive patients, 37 achieved either complete or partial responses for an overall response rate of 70%, not significantly different from the 67% response rate observed among patients unresponsive to hormonal therapy. However, the estimated medial duration of chemotherapy induced response was 23 months for the hormone responsive as compared to 13 months to those unresponsive to hormonal therapy. Similarly, survival time was significantly prolonged among hormone-responsive patients as compared with the non-responsive patients, with estimated median survival times of 33 and 16 months respectively. Their data indicate the nature of the response to hormonal therapy in advanced breast cancer is an important prognostic factor for the results which may be achieved with combination chemotherapy.(481)

Weiss et al stated in 1981 that clinical trials involving hundreds of patients have demonstrated that combination chemotherapy plays a valuable role in preventing recurrence after mastectomy. Although CMF was the first combination tried, other regimens that include prednisone, doxorubicin, tamoxifen or other drugs may supercede this regimen as time allows analyses of their long term benefits and adverse effects. Multimodal treatment has made an impact on the cure of breast cancer, a previously elusive goal.(889)

We have not attempted to cover all the extensive literature on the chemotherapy of breast cancer, but to outline some of the more significant studies and to point out the serious effects such therapy has on the host resistance of the patient. We believe better results may be achieved by combining host-stimulating agents such as mixed bacterial vaccines. These were used very effectively in the small number of breast cancer cases so treated by Coley and others. (See below Part III.) None of these patients developed toxicities or any deleterious sequelae such as a second primary or leukemia.

Cardiac Glycosides

Stenkvist et al reported in 1982 that patients with breast cancer who are receiving cardiac glycosides at the time of diagnosis have a tumor cell population composed of cells that are smaller and more uniform in morphology, density and structure than those on patients not using digitalis.(787) They also found that in patients not taking digitalis the risk of recurrence within five years after mastectomy was 9.6 times that in patients who were taking this drug. These results indicate that cardiac glycosides have a modifying influence on the biologic aggressiveness of breast cancer.(787)

ANTICOAGULANT THERAPY TO PREVENT METASTASES

Factors which may cause or *prevent* the development of metastases deserve greater attention. Unlike the majority of oncologists, the Fishers recognized the importance of this problem and studied it extensively beginning nearly 30 years ago.(259–278) The Fishers suggested that anticoagulants hinder the attainment of an extravascular position by tumor cells. Since there seems to be a relationship between the effectiveness of a chemotherapeutic agent and this extravascular migration, the possibility is considered that anticoagulants may prolong the residence of tumor cells within blood vessels and thus improve the effectiveness of chemotherapeutic or immunotherapeutic agents as adjuvants to surgery.(265)

Evidence supporting the efficacy of anticoagulants in the treatment of cancer is based on results in certain experimental animal tumors. It has been found that the action of the cancer coagulative factor can be blocked in many by anticoagulants. This subject was thoroughly reviewed (93 references) by Zacharski et al in 1979.(927) These various studies indicate that by using anticoagulants it is possible to interfere with tumor growth and the development of metastases.(266;828–832; 926–928)

The ability of primary breast cancer to metastasize is a major obstacle in the search for a cure of this disease which is now killing approximately 35,000 women in the United States each year. The development of a metastasis represents the terminal stage of an intricate series of events in which malignant cells, released from the primary tumor, disseminate to distant sites, by way of the vascular and lymphatic system. Most tumor cells so dispersed die.

Primary neoplasms have a mosaic of cellular potentials, and some of them may have inherent biological properties that guarantee their survival. One of these may be the ability to interact with and attach to platelets, thus enhancing their potential to lodge in the microvasculature and adhere to vascular endothelium. Alternatively, after arrest, tumor cells may initiate the formation of surrounding protective platelet thrombi until extravasation is completed.

The fibrinolytic mechanism is depressed in cancer patients, due to the fact that growing cancer cells produce the cancer coagulative factor which induces clotting.

In addition, many cancers have lost the fibrinolytic activity of the normal tissues from which they arise. Thus, fibrin which is laid down by the coagulative factor in or near cancers is more liable to persist than in normal tissues. This leads to proliferation of capillary blood vessels and connective tissue cells which contribute to the formation of the stroma of tumors and helps to prepare the way for the occurrence of blood-borne metastases.

Michaels in Canada studied the effect of anticoagulants on cancer incidence and survival in 399 men and 141 women who had been on anticoagulants for a total of 1569 patient years.(568) He found the *incidence* of cancer was the same as in the general population, but *the death rate was only one-eighth the expected rate. In addition, no distant metastases developed while patients were on anticoagulants.*

Historically, anticoagulants which have been used include leeches and an extract of snake venom known as ancrod.(402) Modern anticoagulants include dicoumarol, heparin, brinase, warfarin and bacterial enzymes or vaccines.

Leeches: The first empiric approach to this problem was *the use of leeches* by physicians treating cancer patients in the 19th century and earlier.(816) See Part II, Series A, Case 13, for such a case. Eventually, *Hirudin*, the anticoagulant present in the salivary glands of leeches, was extracted. Intravenous injections of Hirudin caused hemorrhages in rapidly growing tissues such as tumors.

Dicoumarol: This anticoagulant was first isolated by Link about 1935 from spoiled sweet hay. In 1940 it was tried clinically.

Heparin: The Fishers found that when 5,000 Walker carcinoma cells were injected intraportally into heparized rats and heparinization was continued for the next 48 hours, no significant alteration in the incidence of hepatic metastases resulted. If however, heparinization was continued for four and seven days only 33% and 17% incidence of metastases was observed in contrast to 81% incidence in the controls. Thus *the duration of anticoagulant therapy is of utmost importance.*

Brinase: Thornes used Brinase (Protease I, a fibrinolytic enzyme extracted from Aspergillus oryzae,) which has a similar action to plasmin and in addition inhibits antiplasmin.(834) Thornes found that induction of enhanced fibrinolysis by *Brinase or streptokinase activated the cellular immune mechanisms in cancer patients* who were previously anergic to a spectrum of agents used to induce hypersensitivity reactions. The effect lasted less than a week but repeated enhancement produced prolonged conversion from the anergic state for up to 12 weeks. This effect may be due to unmasking of membrne phospholipids by Brinase.(828–832)

Warfarin: Thornes also used sodium warfarin and other fibrinolytic agents in a controlled trial of 128 cancer patients combined with chemotherapy. This regime *doubled the two year survival rate, the best results being in the post-menopausal breast cancer patients.*(833) Warfarin treatment increased the congregation of polymorphonuclear leukocytes and later monocytes and macrophages which "tidy up the tumor area."(833–834)

In April 1976 a five year multihospital study was launched to test the hypothesis that warfarin anticoagulation would favorably modify the course of malignancy. The effects of conventional therapy alone are being compared to conventional therapy plus warfarin in patients with carcinoma of the head and neck, lung, colon and rectum and prostate—the commonly encountered cancers in the V.A. hospital system.(927)

Bacterial Enzymes and Vaccines: Tillett was the first to report on the *fibrinolytic activity of human streptococci.* His work led to the use of the streptococcal enzymes streptodornase and streptokinase (Varidase.) It is now believed that these enzymes may have played a

significant role in the dramatic regressions of cancer observed following concurrent streptococcal infections, principally erysipelas. (See below, Part II.) Tillett never used Varidase in the treatment of cancer.

To our knowledge, no one has ever studied the possible anticoagulant effects of the mixed bacterial vaccines developed by Coley (MBV). However, Most reported that Shear's polysaccharide derived from Serratia marcescens (one of the two organisms used for MBV) did prolong clotting time due to a heparin-like effect. This effect was very much weaker than heparin and lacked clinical significance.(591)

See below, p. 105 for the results of a study in Romania using Polidin, a mixed bacterial vaccine combined with heparin in treating tumor bearing mice. The results were significantly better when *both* were used than either alone.(455)

It is hoped that groups such as the National Surgical Adjuvant Breast Cancer Project in the U.S. and the British Breast Cancer Cooperative Groups may undertake cooperative studies on the effects of anticoagulants in treating breast cancer. Chemotherapeutic agents are usually cytotoxic drugs which when successful have a greater toxic effect on the tumor than the host. Immunotherapy and anticoagulants are aimed at enhancing host response to the tumor.(927)

***Prostacyclin*:** Prostacyclin, (PGI_2) a derivative of prostaglandin, was discovered in 1976 by the Wellcome group in England.(579) This microsomal enzyme from blood vessel walls converts prostaglandin (PG) endoperoxides to an unstable substance which is the most potent inhibitor of platelet aggregation yet discovered. It is also a strong vasodilator.(580) Its importance for cancer patients lies in the fact that it helps disperse microthrombi of tumor cells trapped in fine vessels, thus helping to prevent metastases.

Prostacyclin is made by human and animal blood vessels, especially endothelial linings, and it appears to be responsible for keeping healthy arteries free from platelet thrombi.(402) The year that it was discovered it was also synthesized.(580) It was first known as PGX, and then renamed prostacyclin with the abbreviation PGI_2.(579) It's latest name is epoprostenol.

The activity of locally generated PGI_2 in blood vessels is reinforced by circulating PGI_2 released from the lungs thus helping to disperse microthrombi *(including tumor thrombi)* trapped in fine vessels. Hyperventilation increases prostacyclin release, perhaps of importance in exercise and the control of pulmonary ventilation perfusion ratios. The finding that low concentrations of prostacyclin are released from the lungs *in vivo* prompted the proposal that the pulmonary endothelium may be regarded as an endocrine organ regulating platelet behavior.(337)

Decrease in prostacyclin production occurs in several diseases including atherosclerosis and diabetes.(580) In tracing 428 cancer patients successfully treated by immunotherapy with Coley's Mixed Vaccine (MBV), we found a considerable number subsequently developed atherosclerosis and coronary heart disease, causing by far the largest number of deaths. These occurred from 5 to 60 years after recovering from their malignancy.(602–619) We believe that cancer patients may be more prone to atherosclerosis due to decreased prostacyclin production.

PGI_2 is a powerful antimetastatic agent against B16 amelanotic melanoma cells. This effect may result from the platelet antiaggregatory action of this agent, and it is potentiated by a phosphodiesterase inhibitor.

PGI_2 Inhibitors. Metastatic tumor cells may alter the critical prostacyclin-thromboxane balance in favor of thrombosis. Normal PGI_2 production by healthy vascular endothelium may therefore function as a natural deterrent to successful tumor metastases. Thus PGI_2

synthesis may play a vital role in preventing the spread of metastatic disease. *Nicotine* depresses PGI_2 synthesis in isolated hearts.(857) *Estrogen-containing oral contraceptives* also decrease PGI_2 production.

Recent studies have shown that *irradiation* decreases vascular PGI_2 formation with no concomitant effect on platelet thromboxane production.(11) Since radiotherapy is routinely administered for considerable periods, in daily dose fractions, recovery of vascular PGI_2 production may be inhibited for the entire period of radiotherapy.(11) This would favor the development of metastases.

These findings suggest that breast cancer patients should avoid smoking or the use of oral contraceptives. If they are receiving radiation or if they have diabetes or atherosclerosis they require treatment to stimulate PGI_2 production.

PGI_2 Stimulation. Buerger's disease was treated empirically 50 years ago by injections of Coley's mixed bacterial toxins (Streptococcus pyogenes and Serratia marcescens) with complete cure: severe pain ceased at once, gangrenous toes healed, and the patients remained well with no recurrences.(331; and personal communications) This result is now recognized as being due to stimulation by the vaccine of prostacyclin production. Such patients are now receiving synthetic PGI_2 in Poland, England, and the United States.(815)

Breast cancer patients who received these toxins are cited in Part III. Their beneficial results may have been due in part to PGI_2 production.

Exogenous PGI_2. Exogenous PGI_2 may be effective as an adjunct in reducing the total number of metastatic tumor cells that survive vascular dissemination.(402) *PGI_2 and agents that may increase endogenous PGI_2 production or prolong its activity are suggested as new antimetastatic agents.* Concurrent acute bacterial infections and bacterial vaccine therapy (MBV) stimulate the production of endogenous PGI_2.(614) It is time such therapy was again used in the treatment of primary breast cancer in controlled trials, to compare with the results obtained by adjuvant chemotherapy, and in combination with primary radiation therapy to offset the decreaed production of vascular PGI_2 which occurs during radiation.

CASTRATION AND ENDOCRINE THERAPY

Estrogenic hormones are known to stimulate the growth of breast cancer. Originally only about 50% of breast cancers were considered to be affected by the hormonal environment. With new techniques, such as the use of immunoperoxidase, the percentage has increased to between 75 and 85%.(817a)

Castration by surgery or radiation was used first to remove this hormonal stimulus. More recently antiestrogens have been used in estrogen receptor positive patients.

***Surgical Castration*:** A number of comparative studies show that there would seem to be no further justification for prophylactic oophorectomy in the treatment of breast carcinoma.(906) In contrast, the antiestrogens such as tamoxifen or aminoglutethimide have been used increasingly and are effective in the estrogen receptor positive patients.

In 1896 Beatson in Glasgow recognized that human breast cancer was hormonally responsive. This led him to perform prophylactic oophorectomies following mastectomy. Although 35% of the patients were said to have benefited to some degree, the practice was abandoned by 1905. It was reintroduced about 1960. It was not until 1970 that a

good prospective trial of a large series of patients traced up to five years after oophorectomy revealed no evidence that this procedure conferred an advantage of delaying recurrence or preventing death.(742)

In 1972 Segaloff reported another prospective study with random assignment of patients to the oophorectomy and non-oophorectomy groups which has failed to show a difference in survival experience. This, coupled with the fact that we lose the knowledge of whether the tumor is hormonally responsive and then expose many women to a fruitless early interruption of ovarian function, should now discourage the practice.(742)

The traumatic effect of mastectomy upon the patient's immune system is compounded by the further physical trauma of oophorectomy. In addition it is well known that both these operations stir up intense emotional reaction causing serious further immunosuppression.

It is therefore not surprising that in many instances severe exacerbations of breast cancer have occurred after oophorectomy.(906) See below, section on psychological adjustment, p. 117.

***Radiation Castration*:** Ovarian irradiation following mastectomy has been used in England, France and the United States beginning with de Courmelles in 1922.(556) Meakin et al recently reviewed the results and reported on its use with prednisone. They found that in premenopausal women aged 45 years or more, recurrence was significantly delayed and survival prolonged. No value was demonstrated for ovarian irradiation with or without prednisone therapy in postmenopausal patients.

In recent years an overall objective response lasting six months or more was obtained in 27.2% of 527 patients with recurrent inoperable breast cancers who were castrated either by surgery or radiation.(299) However, many breast cancers are virtually independent of the hormonal environment.

HORMONE THERAPY

Factors Affecting Success or Failure with Endocrine Therapy

***Estrogen Receptors*:** The estrogen receptor (ER) content of breast cancers is an important parameter in assessing their possible response to endocrine therapy.(817a) After oncogenesis, the cell may retain all or only a fraction of its usual estrogen receptor sites. If it retains them it is potentially subject to regulation by its hormonal environment. If it does not it will not be expected to respond to endocrine therapy. Utilizing new techniques, such as immunoperoxidase, ER has been reported in 70 to 85% of breast cancers. The percentage has risen from around 50% originally reported.(817a) About 50% of patients with high levels of ER on their tumors respond to endocrine therapy, while those with low or undetectable levels respond in only 8%.

Kinne et al found that ER-positive (ERP) patients tended to have a lower recurrence rate and had significantly improved survival. The difference was most apparent in patients with four or more axillary nodes involved. ERP patients who recurred also had a better survival, ER did not influence response to adjuvant chemotherapy.(454)

Hilf et al analyzed the value of ER analysis in primary breast cancer as a potential prognostic factor in three clinical situations: time to recurrence in patients with no therapy after mastectomy, failure of patients receiving adjuvant therapy and response of advanced

disease patients to cytostatic chemotherapy. In none of these clinical settings were they able to demonstrate the usefulness of ER status as prognosticator of the disease course or its response to therapy.(384)

McGuire (1978) concluded that the use of cytoplasmic ER to help select patients with advanced breast cancer for endocrine therapy is well established and whenever possible should be part of the routine evaluation. Other potential uses are emerging.(524) The data suggest that ER determination on the primary tumor may be very important in designing new adjuvant trials. In addition, several groups are investigating the role of ER in selecting patients for chemotherapy. The presence of progesterone receptor in a tumor signals the presence of a higher ER content and a very likely favorable response to endocrine therapy.

Obesity: A significant association between body weight and estrogen receptor protein was noted in 83 women with primary and metastatic breast cancer. 54% of these women weighing over 150 pounds had low or absent receptor protein vs. 25% of those under 150 pounds suggesting that in heavier women the endocrine and metabolic milieu favors autonomous growth of breast cancer and adjuvant therapy should accordingly be planned.(650) See above, pp. 25 and 30.

One possible reason why adjuvant chemotherapy appears to benefit premenopausal women more than older women may be that the drugs *impair ovarian function and thus suppress the production of prolactin.*(518) Prolonged chemotherapy, especially if the regimen includes an alkylating agent (e.g. cyclophosphamide) induces ovarian failure in a high percent of premenopausal women. Amenorrhea is permanent in about 79% and reversible in the remainder. *It appears that chemotherapeutic castration is distinctly superior to surgical or radiological castration as regards relapse rate and overall survival.* (Bonadonna, to be published.) For a discussion of prolactin see above p. 13.

Anti-Estrogens

Tamoxifen: This anti-estrogen has been used in treating advanced or recurrent breast cancer for over eight years with no deaths in over 10,000 patient years' experience. There have been 12 major studies of 988 patients with only 27 withdrawals, due mainly to emesis and nausea (few of these reactions were ever severe.) A mean duration of response greater than one year has occurred.(320) Many patients are on continuous therapy for four years without long term problems, except for the possibility of atherosclerosis. However, the mechanism is not clear. This agent is neither mutagenic nor teratogenic in animals. It is given orally.(420:655;873;874) At a dosage of 10 mg. twice daily, 60% of patients showed arrest or regression of tumor growth. At 20 mg. twice daily 77% showed this response. No patients showed virilization or fluid retention.

In a Scottish trial of tamoxifen the overall response rate was 53% and 28% achieved complete remission, the mean duration of response being 24 months. The highest response rate was found in patients with lymphatic recurrence. The drug was well tolerated.(643)

Ward et al reported that relief of bone pain due to metastases occurred in 8 out of 19 patients. Tamoxifen now appears to be established as a useful and safe treatment for advanced mammary cancer.(874) It is now being studied as an adjuvant agent in the initial treatment of breast cancer in the National Surgical Adjuvant Breast Program in the United States.(874)

In addition to being a powerful anti-estrogen, tamoxifen is a potent inhibitor of prostaglandin (PG) synthesis and this factor may contribute to its efficacy in the treatment of

breast cancer or its metastases, including the relief of bone pain. Female sex hormones can stimulate PG synthesis.(52)

Since 1972 the National Surgical Adjuvant Breast Project has studied the possibility that the addition of tamoxifen to L-phenylalanine mustard combined with 5-fluorouracil enhances the benefit of these two drugs in women with breast cancer and positive axillary nodes.(271) The risk of recurrence is present during the first two years after operation. Recurrence was reduced at two years in patients given the three drug regimen whose tumor estrogen levels were ≥fmol. Among patients ≥ 50 years old treatment failure was significantly reduced by 51% in those with one to three positive nodes and by 64% in those with four or more. Higher receptor levels were associated with greater probability of disease-free survival. Patients under 49 were less responsive. This adjuvant chemotherapy is not indicated in patients under 49 whose tumor receptor levels are below 10 fmol. There is a suggestion of benefit in patients over 50 whose levels are low.(271)

Glick et al concluded that inability to determine estrogen receptor status should not prejudice against the use of tamoxifen in postmenopausal patients with advanced breast cancer. No benefit was seen from the addition of CMF chemotherapy in tamoxifen responders.(320)

Nemoto et al stated that hypercalcemia must be recognized as perhaps the most serious side effect of tamoxifen citrate. Particularly in patients with bone metastases, close attention to the calcium level must be paid during the first seven to ten days of tamoxifen therapy. Hypercalcemia is usually mild and transient.(622)

Another side effect, recently reported in a 57 year old woman, is that high dosage tamoxifen produced retinopathy characterized by white superficial refractile retinal lesions 3 to 10 microns in diameter in the macular area, 30–35 microns in diameter in the paramacular area. The smaller lesions were intracellular and the larger ones extracellular. They seemed to represent products of axonal degeneration.(435a)

Tamoxifen (Nolvadex) for Early Breast Cancer: In 1977 the Nolvadex Adjuvant Trial Organization launched a prospective multicenter randomised trial to evaluate the effect of tamoxifen as an adjunct to local treatment for patients with operable breast cancer. 1,131 patients were recruited and after modified radical or simple mastectomy and axillary node sampling with radiotherapy for node positive cases, they were randomised to no other treatment or to tamoxifen (10 mg. twice daily for two years). By August 1983 significantly fewer deaths have occurred in the tamoxifen group compared with the controls (31% reduction.)(45)

Flurbiprofen: This is another PG inhibitor which has been used experimentally and which appeared to prolong survival time in tumor bearing mice. The improved therapeutic effect when flurbiprofen is combined with radiotherapy and/or chemotherapy indicates that inhibitors of prostaglandin synthesis may be valuable adjuncts to the treatment of cancer.(52) Studies might be undertaken to determine whether women at high risk of breast cancer due to heredity, synthesize more PG than normal. (See above p. 127–129 for discussion of *prostacyclin* which is beneficial in its effects on cancer patients.)

Bromocriptine: Grisoli et al reported a spectacular regression of brain metastases from breast cancer treated by bromocriptine (7.5 mg. daily for 18 months.) She became asymptomatic with negative cat scan six months after this treatment was begun.(335a)

Nemoto et al also noted that response rates to hormonal modalities such as tamoxifen are reduced in women with metastatic breast cancer who have previously received combination chemotherapy.(623a)

Aminoglutethamide: Originally introduced as an anticonvulsant in 1960, was later found to block adrenal steroid synthesis, including estrogen production. It has therefore been used as an antiestrogen in breast cancer patients.(376;731)

Aminoglutethamide(A.G.) (250 mg. four times daily) produced objective tumor regression in 38% of 50 patients without regard to estrogen receptor status and in 10 of 21 women treated with an A.G. arm of a randomized trial of this agent vs. hypophysectomy. The response rates in these two groups appeared to be similar.(729)

This drug plus hydrocortisone used in a randomized trial comparing it with surgical adrenalectomy in 86 postmenopausal women since it is an adrenal inhibitor.(732) This study indicates that medical therapy with A.G. and hydrocortisone may be logically chosen in place of surgical adrenalectomy.(730;732) Hydrocortisone alone may be very helpful in treating hyperalgic bone metastases. This may be just as effective as adrenalectomy and is produced at less cost. It produces palliation without virilization and can be administered orally.

The mechanism of action of A.G. in breast cancer patients is not solely its inhibition of cholesterol to pregnenolone conversion in the adrenal. An additional action is the blockade of estrogen synthesis outside the adrenal gland. Nearly all the estrogen produced in postmenopausal women can be accounted for by the extra-adrenal pathway: androstenedione-to-estrone conversion (aromatization.) The enzymes required for this are present in fat tissue, liver, muscle, and also in some mammary tumors. A.G. is an extremely potent inhibitor (95–98%) of aromatization and thus of extraglandular estrogen production in postmenopausal breast cancer patients. Thus, by blocking both adrenal prehormones and estrogen synthesis in extraglandular tissues (and perhaps in the breast cancer itself,) A.G. can lower the plasma estrogen levels nearly to those observed in adrenalectomized patients.

A.G. then, is a unique drug which blocks estrogen production by both an adrenal and an extra-adrenal mechanism. It provides a new and alternative approach to the treatment of patients with recurrent metastatic breast carcinoma.(732)

Progestins

The name progestin (originally used for the crude hormone of the corpus luteum) is now used also for certain synthetic or natural progestational agents.

Progestins have been tested for anti-tumor activity in breast cancer patients since the mid 1950's. Medroxyprogesterone acetate (MPA), a synthetic C-21 progestin, was developed in 1958 and shortly thereafter became the most commonly used progestin agent for treating advanced breast cancer.

In 1981 Lober et al in Denmark reviewed the subject and concluded that only limited data are available concerning response rate in relation to dose and route of administration. In view of the modest side effects (principally amenorrhea and weight gain), and the clinical and theoretical evidence of a mode of action different from other endocrine therapies, future controlled studies are warranted to establish the therapeutic efficiency of progestin therapy in primary and advanced breast cancer.(506) Present evidence suggests a meagre response rate of approximately 10 or 15%.

HYPERTHERMIA

This section will outline the history and present use of hyperthermia in the treatment of breast cancer. The modalities used include cautery, (live and electrocoagulation), sauna, microwaves, and non-ionizing electromagnetic radiation. Also other investigators are using whole body hyperthermia induced by hot water, hot air or hot paraffin. The potentiating effect of various forms of hyperthermia on the response to radiation and chemotherapy are also discussed.

The beneficial effects produced in cancer patients by bacterial infections or vaccines may be due in part to the fever they induce. The most dramatic results were observed in patients with marked febrile reactions, (see below Part II and III.)

Cauterization has been used as a therapeutic agent for cancer since 2000 B.C.,(624) and all through the 18th and 19th centuries reports appeared describing the beneficial effects of heat on cancer. Tanchou, a distinguished 19th century physician in Paris, collected 300 cases of inoperable breast cancer which had been treated medically. In many of these cases heat was employed; in many others fever occurred due to infections such as erysipelas, followed by complete or partial regressions.(816)(See below Part II for such cases.)

Westermark reported that recurrences after breast cancer surgery were much less frequent following the *electrocautery* knife than after ordinary surgical removal even when only an incomplete removal could be made.(896)

Kolischer recognized that electrocoagulation not only produces mechanical destruction of the tumor, but helps to immunize the patients against further progress of the disease by an intense stimulation of the reticuloendothelial system and the consequent local and general action of the macrophages.(460) He noted that the combination of radiation and electrocoagulation showed a more pronounced improvement than radiation alone.

In Finland where *hot sauna bathing* is a common practice, the incidence of breast and testicular cancer is lower than in neighboring countries where the sauna is not used. The end results in Finland following lumpectomy and relatively low doses of irradiation for breast cancer are better than in other countries using more radical surgery and radiation.(599; 600) Since we now know that heat and fever potentiate the response of tumors to radiation, and stimulate the immune defenses, such results are not surprising. Many surgeons and radiotherapists are now using various forms of hyperthermia alone or as an adjuvant to surgery and radiation with encouraging results. Accessible tumors such as breast cancer are particularly amenable to such treatment.(558; 608; 613)

In this connection it is of interest to cite the unusual report of Eason in 1776, which is given in detail in Part II, Series H: an extensive inoperable breast carcinoma regressed completely after the patient was struck by lightning!

It has been demonstrated that when hyperthermia is induced in a tumor embedded in a normal tissue the tumor will be heated to a higher temperature than its immediate environment. This stems from the changes effected by heat in the thinwalled and irregular neovasculature of the tumor. At 41°C. during the initial heating phase, there is temporary vasodilation, but at 42°C. vasoconstriction, stasis, hemorrhage and thrombosis take place with slow or complete shutdown of microcirculation. Consequently, while the heat-induced vasodilation in a normal tissue leads to heat dissipation, tumors become repositors of heat. Further hypoxia, decrease in pH and necrosis follow, thus increasing the lethal effects of hyperthermia on the tumor cells.

Beginning in 1976 a group at Duke University Medical Center has used local *microwave hyperthermia* at 42°–43.5°C. for 45 minutes immediately following radiation. This yielded

favorable therapeutic results, occasionally dramatic. Among their cases was a 30 year old woman with extensive chest wall recurrence and bone metastases six months after radical mastectomy for infiltrating duct carcinoma. The disease regressed rapidly but incompletely following palliative irradiation (cobalt 60, 2,800 rad.) She returned eight months later with friable ulcerating right chest wall disease $12 \times 12 \times 6$ cm., progressive despite intensive chemotherapy.(849, Fig. 3) Using opposed tangential cobalt fields, 2,000 rad T.D. was given in 10 fractions over 14 days; 2,450 MHz microwave heat was applied on alternate days for six sessions, with tumor temperature of 43–44°C. for 40 minutes per session. Tumor regression was apparent from day to day, and substantial palliation was achieved. One month after treatment, total tumor slough was observed, although adjacent untreated tumor had progressed.(849, Fig. 4)

This group has continued to use local microwave hyperthermia following ionizing radiation (200–600 rad two to five times weekly to a total of 1,800–4,200 rad in 5 to 14 fractions.) Hyperthermia (42–44°C.) was given two to three times a week (maximum 10 sessions in four weeks.) Among the 19 patients treated were five advanced breast cancers with extensive chest wall recurrences. Tumor regression was apparent from day to day in some cases. This team concluded that "local microwave hyperthermia in combination with radiotherapy offers the possibility of substantial impact on clinical cancer therapy, whether of curative or palliative intent."(849)

In reviewing the numerous articles recently published regarding the use of hyperthermia in the treatment of malignant tumors it is difficult to find mention of the application of this method in the treatment of breast cancer, except in a few reports such as the one just cited. However, breast cancer would appear to be a particularly good target for treatment with local hyperthermia alone or in conjunction with other therapeutic modalities.

Non-ionizing electromagnetic radiation of various frequencies is one of the most effective methods of generating heat in tissues.

The breast, being in large part composed of fat, a low water content tissue, can be easily penetrated by microwave radiation which can then become selectively absorbed by the tumor and result in induction of heat. The impaired blood supply characteristic of most malignant tumors will further contribute to maintaining the desired higher temperature in the tumor mass. The topography of the breast permits easy access to the tumor. Most lesions can be easily delineated and focusing of microwave energy can be accomplished by appropriate applicators and cross-fire beams.

The success of hyperthermic treatment of malignancies is closely related to the ability to deliver uniform heat to specific volumes of tissues and to maintain the optimal temperature for a desired period of time.

This problem has been satisfactorily solved by the cooperative effort between the RCA Microwave Laboratories and a group of investigators in the Radio-therapy Department, Montefiore Hospital, New York. A series of applicators has been designed to fit specific tumor and organ geography and has proved highly satisfactory in preliminary trials in animal(557) and human tumors.(558)

Mendecki et al achieved 100% eradication of mammary adenocarcinoma in C3H mice and long term survival following four treatments at 43°C. for 45 minutes induced by a 2,450 MHz generator.

Among patients treated with microwave-induced local hyperthermia in conjunction with radiotherapy, there were several with primary or locally recurrent breast carcinoma. An average treatment course consisted of application of heat to 43°C. for a period of 45 minutes, followed by radiation twice weekly for six to eight sessions. Lesions so treated

regressed faster and more completely than similar lesions given radiation alone, and this usually occurred with a lower radiation dose.

There is, at present, ample evidence that hyperthermia acts as a sensitizer to radiation.(910) When combinations of the two treatment methods are applied a lower radiation dose is sufficient to produce lethal damage to the tumor.

The synergistic effect of radiation and heat is based on the following observations:

1. Heat effectively destroys radioresistant hypoxic tumor cells and decreases oxygen enhancement ratio (OER.)(213;216;694;710)
2. Cell heating interferes with the repair of radiation induced sublethal damage.(645)
3. Cells in the S-phase of the cell cycle, most resistant to radiation, are effectively destroyed by heat.(897)

In view of these considerations the Montefiore group proposed that susceptible tumors, such as breast cancer, be subjected to the following treatment protocol: 43°C. hyperthermia to be delivered for a period of one hour by microwave apparatus. After the first 15 minutes of treatment the calculated radiation dose is to be simultaneously administered, usually for 3–6 minutes, followed by the remaining period of hyperthermia. The development of thermal tolerance will preclude more than twice weekly treatment sessions. The number of treatments must be individualized. When this protocol is not feasible, radiation should be given first and hyperthermia started as soon as possible thereafter.

For deep seated lesions such as metastases to the lungs or primary lung cancer, *radiofrequency heating* is now being used in this country, in Europe and in Australia, using specially designed equipment and careful monitoring of the temperatures produced in the tumor and normal tissues.(488;910)

Other investigators are using *whole body hyperthermia induced by hot water, hot paraffin, hot air,* etc.(910) Recent studies indicate that whole body hyperthermia produced by such regimens may be immunosuppressive. The appearance of metastases was advanced in whole body heat-treated mice as compared with those given local hyperthermia.(920) Certainly patients prefer the local applications which do not require anesthesia which in itself is immunosuppressive. The fact that hyperthermia can *potentiate the response to radiation* and help destroy the relatively radioresistant hypoxic cells is of special significance to radiotherapists.(452;910)

It is now apparent that hyperthermia also *potentiates the response of tumors* to chemotherapy.(461) Thus there appears to be a potential for combining hyperthermia with drugs.(347) The interaction with hyperthermia (41–45°C.) and chemotherapeutic agents frequently results in increased cytotoxicity over that predicted for an additive effect, although to date a very limited number of drugs have been examined for such a possible interaction.

Hahn et al noted a striking synergism in the cytotoxicity of 42–43°C. hyperthermia combined with either bleomycin or adriamycin in mammary sarcoma in mice. Whatever the mechanisms involved, the synergism of the two modalities could prove useful in the chemotherapy of solid tumors in man.(347)

At 42°C. the upper limit useful for whole body hyperthermia the most promising agents of those tried to date appear to be the nitroseureas and cisplatinum. Insufficient data exist for cyclophosphamide, whose long half life makes it an attractive candidate. Localized heating seems optimum at higher temperatures (43–45°C.) No data exist in the literature on possible "thermic sensitizers," i.e. drugs that are noncytotoxic at 37°C. but become effective at elevated temperatures. Two special cases are adriamycin and actinomycin D. They may be contraindicated for clinical use with hyperthermia since not only synergism, but also protection by hyperthermia have been demonstrated, depending upon the time-sequence relationships of the heat and drug treatments.(346)

We believe that fever induced by injections of bacterial vaccines (MBV) may prove more effective than whole body hyperthermia produced by hot air, hot water or oil.(613;614) Such therapy also increases the local heat of the tumor or its metastases above that of the rest of the body.(614)

In conclusion, there is at present ample evidence that hyperthermia alone, or as adjuvant to other agents, has a definite potential in the treatment of breast cancer and that the adoption of this method is only a matter of more extensive clinical evaluation and improved technical approach.

IMMUNOTHERAPY

Introduction

It is now apparent that cancer patients can mount an immune response similar to that which accompanies infectious diseases. Thus we stand on the threshold of a new era in the understanding and treatment of cancer, based on immunological concepts, comparable with the era which witnessed the conquest of many infectious diseases, including poliomyelitis.

As Smithers stated long ago, the weight of clinical evidence demands that we regard the cancer cell merely as a cell behaving abnormally, and, if we cannot remove it, that we direct our treatment as much to influencing the environment in which it is expressing its abnormal behavior as to altering its activity or attempting its destruction.(771)

There are three major forms of immunologic activity. The first to be discovered was the antibody response, now known to be produced by B cells that are manufactured in the bone marrow and differentiated into plasma cells that produce antibody. This occurs as a result of direct or indirect stimulation by circulating antigen, and the response is highly specific.

Next to be revealed was the cellular immune response. Lymphocytes (or T cells) which mature in the thymus and reside in lymphoid tissue, are released into the circulation upon stimulation by antigen. They destroy the offending cells on contact, through cytotoxic activity. Stimulation of T cells may be direct, but often require that the antigen be processed by macrophages.

A third immunologic component, consisting of natural killer (NK) cells, was discovered relatively recently, from observations that animals have some natural resistance to tumors. This resistance is not mediated by B or T cells. The process is different from immunity acquired by previous exposure. It can be enhanced or suppressed, but not very greatly; immunization, then, is rather ineffectual in stimulating NK cell immunity. It is stimulated by viral infections, possibly through production of interferon. This obviously has serious implications for humans, since antigenicity is a prerequisite for an immunologic approach to cancer control.

Morton believes that immunotherapy is a logical adjunct to cancer therapy. Immunological competence in patients whose tumors can be removed surgically is far stronger than in patients with widespread disease.(587) The surgeon is ideally suited to use immunotherapy before and after the operation for breast cancer, and such a combined approach will permit more conservative procedures. However, in the majority of women with carcinoma of the breast, the disease is already disseminated at the time of initial presentation. Although occult metastases are not always detectable even with modern imaging techniques, the long term follow up studies confirm that the majority of women with breast cancer treated by conventional methods ultimately die of their disease.(909)

Treatment of the regional nodes by ablation or radiation may cripple these important components of the immune response. However, if immunotherapy is given to stimulate the lymphoid tissues to greater activity the opposite result may be achieved: increased effectiveness of the immune response.

To be most effective in stimulating the lymphoid tissues in breast cancer patients, and thus help prevent recurrence or metastasis, immunotherapeutic agents such as mixed bacterial vaccines (MBV) should be injected intradermally along the pectoral major muscle, along the third digitation of the serratus muscles and along the anterior axillary line at the edge of the pectoral muscles. These areas are of special importance for tumors of the outer quadrant and those extending through the breast.

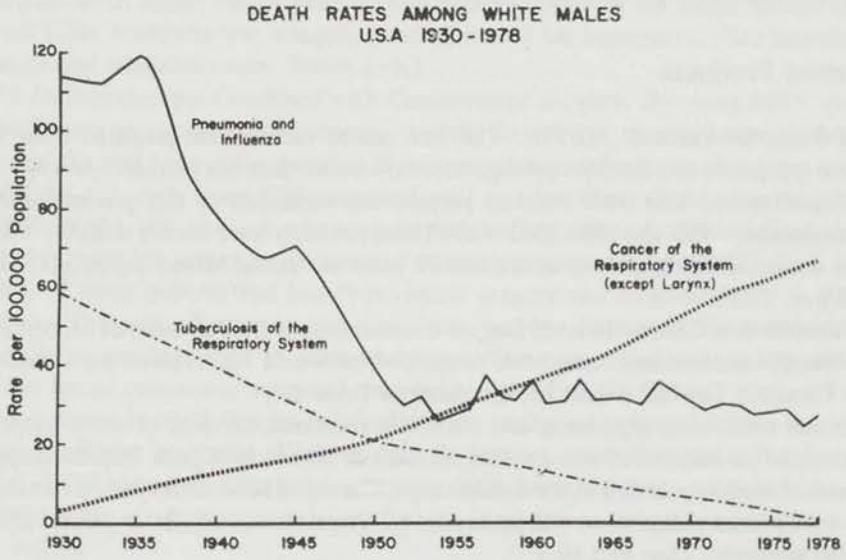
For the deep axillary nodes, the subpectoral, infraclavicular and subclavicular or humeral nodes, injections intradermally over these regions should be tried. Also inject throughout the pectoral muscle to disseminate the vaccines through the intermuscular trunks to reach the supra- and infra-clavicular nodes.

Until recently, the prevailing view of cancer among physicians as well as laymen, has been that of an inexorably progressive disease, the only hope of successful treatment being eradication of every malignant cell by surgery, radiation, chemotherapy or some combination of these.

Although there have been strong indications that this is not always true, and that cancers are frequently under some form of restraint, only in the last 25 years has sound evidence for this been forthcoming. This evidence, scattered through the medical literature for over 200 years, had never before been assembled and analyzed in the light of modern research.(291–295;571;602–619) *Recognition that immunological reactions do occur against cancer, not only in animals, but also in man, is of great importance for the present and future treatment of all cancer.*

Epidemiological Background

Epidemiological data assembled in the past 45 years indicates that in developed and developing countries the incidence of *infections is decreasing* at the same time that the incidence of *cancer is increasing*. An example of this is illustrated in Fig. 1, with figures



furnished by the National Cancer Institute for mortality from lung cancer and pulmonary infections in the United States from 1930–1978. The increasing exposure to carcinogens present in cigarette smoke occurred in the period in which the protective host-stimulating effects of respiratory infections had been largely eliminated.

Meyer and Benjafeld postulated that a contributory factor to the increase in cancer might be the widespread use of antibiotics since 1940. "Antibiotics may absolve the body of the need to bring the normal immunological mechanisms into use—a mechanism that has been acquired through millions of years of evolution."(561)

Microbial Immunological Modifiers

***Bacterial Infections, Spontaneously Contracted*:** Nature produced the first form of immunotherapy when cancer patients accidentally contracted an acute concurrent bacterial infection. It is fortunate that the medical literature recorded such cases and we have therefore been able to assemble a total of 449 such cases, some of which were unpublished.(611–614) The majority of these so called spontaneous regressions occurred following streptococcal infections, principally erysipelas. However, the majority of permanent results occurred after infections described as "wound infection, suppuration, abscess, sepsis." Most of these appeared to be in the region of the tumor and much more *prolonged* than the usual 10 to 15 days duration of an erysipelas infection. Of these 449 cases, 93 were mammary cancers and are included in the present study. (See Part II.)

***Bacterial Infections, Induced*:** We also studied the cases in which physicians attempted to induce bacterial infections as a therapeutic measure in breast cancer patients and we found 18 such cases, beginning with Schwenke's in 1774. These are abstracted in Part III, Series D, E, and F.(613;614;816)

Coley was the first to do so in this country in 1891.(148) He and others in Europe soon found that using inoculations of living cultures of streptococci or staphylococci to induce infections in cancer patients was not practical because living cultures could not be controlled: they were often avirulent or too virulent.(148) This led Coley to develop a vaccine which would avoid these problems.(149–156)

Microbial Products

***Mixed Bacterial Vaccine (MBV)*:** This first mixed vaccine was prepared from Streptococcus pyogenes and Bacillus prodigiosus, now called Serratia marcescens. (149–156) Both filtration and heat were used to prepare the variations of this product available between January 1893 and 1983.(602–619) These products were known as Coley's Mixed Toxins during his lifetime, but in the last 30 years are called Mixed Bacterial Vaccines or MBV.

MBV for Breast Cancer: In analyzing all microscopically proven cases of cancer treated by MBV, 896 determinate cases were found(614) of which 78 involved the breast. (See below Part III.) The end results are tabulated in Table 1.

In addition to causing regression and markedly increased survival in some inoperable breast cancer patients, there was marked decrease or cessation of pain, improved appetite and marked weight gain and in some cases regeneration of bone destroyed by metastases. In advanced cases reduction or disappearance of lymphedema, ascites or pleural effusion was also observed. (See Part III.)

TABLE 1.
5-YEAR SURVIVAL OF 896 PATIENTS WITH VARIOUS TYPES OF TUMORS TREATED WITH MIXED BACTERIAL VACCINES (MBV)

Type of Tumor	Total No. of Cases	5-Year Survival Inoperable No.	%	Operable No.	%
Bone Tumors					
Ewing's Sarcoma	114	11/52	21	18/62	29
Osteogenic Sarcoma	162	3/23	13	43/139	31
Retic. Cell Sarcoma	72	9/49	18	13/23	57
Multiple Myeloma	12	4/8	50	2/4	50
Giant Cell Tumor	57	15/19	79	33/38	87
Soft Tissue Sarcomas					
Lymphosarcoma	86	42/86	49	—	—
Hodgkin's Disease	15	10/15	67	—	—
Other Soft Tissue Sarcomas	188	78/138	57	36/50	73
Gynecological Tumors					
Breast Cancer	33	13/20	65	13/13	100
Ovarian Cancer	16	10/15	67	1/1	(100)
Cervical Carcinoma	3	2/3	67	—	—
Uterine Sarcoma	11	8/11	73	—	—
Other Tumors					
Testicular Cancer*	64	14/43*	34	15/21	71
Malignant Melanoma	31	10/17	60	10/14	71
Colorectal Cancer	13	5/11	46	2/2	(100)
Renal Cancer (adult)	8	3/7	43	1/1	(100)
Renal Cancer (Wlms' Tumor)	3	—	—	1/3	33
Neuroblastoma	9	1/6	17	2/3	67
TOTAL	896	238/523	46	190/373	51

*including 16 terminal cases

The number of breast cancer patients who received MBV is not large, but the results achieved if the treatment was adequately administered are impressive. (See introduction to Part III and tabulated cases, Series 1–5.)

MBV Immunotherapy Combined with Conservative Surgery: By using MBV therapy as an adjuvant to *conservative* surgery, in order to prevent recurrence or metastases, Coley was the first to avoid amputation in patients with neoplasms involving the extremities. Of the 128 such cases 57% remained well and free from disease as compared to only 32% of the 166 cases in which amputation *was* performed. The excellent results achieved in operable breast carcinoma and sarcoma are reported in Part III.

A few of these patients had less than radical surgery and received MBV to prevent recurrence. This was achieved in all but one case, and her disease did not reactivate until 12 years later, causing death 14 years after onset. One patient had no surgery and under MBV her breast carcinoma regressed completely. (See Part III, Table 1, Case 6.)

Morton stated in 1973 that he believed a wide variety of substances have the ability to enhance cellular immunity. These include C. parvum, staphylcoccus, mixed bacterial vaccines, BCG and some of the polynucleotides.(588) He noted that much better immunity is induced if these substances are injected at the same site as the growing tumor or with tumor antigen.

We must now stimulate interest in the development of various mixed vaccines, not merely the one originated by Coley, utilizing several strains of bacteria including those to which patients may have had prior exposure so as to elicit the most effective responses. Such therapy is non-toxic, and the febrile reactions they elicit are beneficial. As noted above such treatment causes stimulation of the hematopoetic tissues and the reticuloendothelial system. It increases the production of interferon and prostacyclin, activates macrophages, causes rapid healing of wounds and ulcerated areas and regeneration of bone destroyed by metastases or surgery.(291–295;571;602–619) It also causes marked relief of pain due to stimulation and release of endorphins. These beneficial effects are less evident if treatment is not begun until after immunosuppressive therapies have been administered or the disease is very far advanced.

MBV Immunotherapy Combined with Radiation and/or Chemotherapy: When MBV is begun prior to radiation, the response of the tumor is enhanced while protection of normal tissues occurs. Recent studies indicate that the response to chemotherapy is also increased by bacterial vaccines, fever and hyperthermia.

Many of the *inoperable or terminal* breast cancer patients treated after Coley's death in 1936 received MBV *after* having had radiation and/or chemotherapy (Part III, Series 3, 4.) Although no cures were obtained, marked palliation, regression, decreased pain, ascites and weight gain occurred in many of these patients.

Klein noted that immunological intervention contributes to the control of established lesions as well as diminishing the likelihood of subsequent metastases. He found that combinations of chemotherapy and immunotherapy are more effective in controlling cutaneous metastases than single modalities.(457)

Recently some oncologists have employed pulsed regimens of high dose methotrexate with citrovorum rescue which allows recovery of immunocompetence and immunologic intervention between successive chemotherapeutic treatments.(219–222) Such therapy should now be tried combined with MBV immunotherapy.

Immunotherapy for Metastatic Lesions: The studies of Edmund Klein et al have shown that local immunotherapy results in a high five-year cure rate of multiple epidermal tumors. *Regressions of metastatic lesions of breast cancer involving the skin and soft tissues have also been observed.*(457)

Onset of pain anywhere in a recovered case should be regarded as indicating the presence of metastasis and bacterial vaccine therapy should be resumed at once and given persistently for at least four to six months. The competence of the immune system may be critical in achieving cancer cure, hence the need, not only to destroy the primary or the metastatic lesions but to strengthen the immune system sufficiently to prevent further reactivation of the disease.(613;614;617)

The inoperable or terminal breast cancer patients who received MBV are found in Part III, Series 4 and 5.

Significant Factors Affecting Success or Failure with MBV: Analysis of nearly 900 detailed histories of microscopically proven cancers so treated indicate that the essential factors were:

1) Stage of disease and/or magnitude of tumor burden.
2) Immune competence of the patient.
3) Potency of vaccine preparations.
4) Site of injection, i.e. close contact with tumor cells, wherever possible.
5) Dosage, frequency and especially duration of injections.
6) Timing in relation to surgery, radiation and/or chemotherapy.
7) Febrile reactions.

These are discussed as follows.

Stage of Disease: As indicated above and below, patients in the earlier stages of the disease responded better to MBV than those with inoperable or metastatic lesions. However, the marked benefit as regards palliation and occasional complete regression in these advanced cases warrants further clinical studies.

Immune Competence: If patients have been immunosuppressed by extensive surgery, prolonged radiation or chemotherapy, or advanced age, their response to MBV or other forms of immunotherapy is compromised.

Potency of the MBV Preparations varied considerably and when the weaker commercial products were used without compensating with increased dosage, the results were much less beneficial.(291–295;571;602–619)

Site: In using chemotherapy the oncologist attempts to attain an inhibitory level of the agents at the site of the tumor. In immunotherapy we should also inject the agents used at least part of the time into the tumor area or areas which can activate the regional lymph nodes to greater capacity. Such a technique helps to increase the antigenicity of the tumor, to elicit an inflammatory reaction and to activate macrophages.

The following investigators have also noted the great importance of site of injection using other bacterial vaccines.

Baldwin noted that extensive animal studies show that *infiltration of agents such as bacterial vaccines and BCG directly into tumor deposits produces a tumor suppressive response whereas in many cases little or no effect is obtained when the agents are injected systemically remote from the tumor.*(35)

Sadler et al found that after subcutaneous injection of radiolabelled Corynebacterium parvum, the majority of the labeled material was detected at the site of injection and little was found in other tissues, whereas with i.v. or i.p. injection highest counts were recorded in the liver.(724)

Ojo et al found a striking difference in the impact of C. parvum on the mouse immune system against murine tumors, depending on the route of administration. Intraperitoneal injections resulted in a dramatic increase in the cytolytic ability of the peritoneal exudate cells. These lytic cells were all found to be natural killer cells. Spleen cell population from intravenously treated mice demonstrated a significant reduction in T lymphocyte function, which could be corrected by removal of suppressor cells.(636)

Yamagishi et al reported that *intraperitoneal* administration of streptococci either prior to or after tumor inoculation reduced neoplastic growth, while *subcutaneous* inoculation of streptococci prior to tumor inoculation did not influence tumor growth. *Thus therapeutic effects of this vaccine depended upon the route and/or timing of administration.*

Host response to streptococci was reduced if surgery was performed shortly before tumor inoculation. However, if it was performed three days after tumor inoculation, the adjuvant action of these vaccines was not altered. The failure to achieve an immunotherapeutic effect in splenectomized hosts suggests that *the spleen was essential for the action of the streptococcal vaccine.*(918)

Dose: A weak immune reaction, elicited by too small a dose of MBV, given remote from the tumor intramuscularly or subcutaneously, may actually stimulate the target tumor cells rather than inhibit them.(680)

Frequency and Duration: Many physicians using MBV were unaware of the need to give the injections aggressively, at least three times a week initially. What was even more important they did not usually recognize the need of continuing the injections for at least four to six months, tapering off the frequency to one a month after the fourth month.(291–295;571;602–619)

Timing: If vaccine therapy is only begun after the disease is very far advanced, significant palliation may occur. This occurs even though the patient's already inadequate immune defenses have been further suppressed by radical surgery, heavy radiation and chemotherapy, but except in rare instances one cannot expect to achieve complete control.

There is a real need for immunotherapy especially as an adjunct before and after conservative surgery.(342) It is particularly needed in all postmenopausal women to augment their response to adjuvant chemotherapy. It should be given in courses before and during the time when recurrence or metastases are most likely to develop. In inoperable cases it can be used to help decrease the tumor burden and protect against the deleterious effects of radiation and chemotherapy while potentiating the response of the tumor to these modalities.

The vital importance of technique of administration is now recognized, especially the need to elicit adequate febrile reactions consistently. When given aggressively, the rapid change in temperature suppresses the ability of neoplastic cells to adapt to higher temperatures. We now know that slow heating seems to induce thermal tolerance in some neoplasms. Unfortunately, many patients in the past received inadequate doses of MBV given intramuscularly or subcutaneously producing slowly rising temperatures.

Febrile Reactions: Patients receiving MBV had a significantly higher percentage of complete and permanent regressions if marked febrile reactions averaging 39–40.5°C. were elicited, especially the inoperable cases. Injections given in or near the tumor or intravenously or larger doses given intramuscularly elicited these reactions. *The subcutaneous route was least effective.*(291–295;571;602–619)

It is of interest to note that the largest number of dramatic so-called spontaneous regressions of cancer occurred following an acute febrile infection.(611)

Bacterial Pyrogens vs. Whole Body or Local Hyperthermia: The available evidence suggests that modern whole body hyperthermia produced by hot air, or immersion in hot water or hot paraffin usually requires immunosuppressive anesthesia or tranquilizing agents. Some of these heroic procedures may in themselves be immunosuppressive.(920)

On the other hand, local hyperthermia by radiofrequency or by regional perfusion of heated fluids seem to offer greater promise and is better tolerated by the patient, without any immunosuppressive effects. Neither type appears to provide sufficient duration of therapy to insure permanent results.

We believe that even better immediate and final results may be possible by judicious use of local hyperthermia given weekly combined with injections of MBV, not only Coley's formula, but other types given at least two or three times a week at first. These injections must then be continued after the local hyperthermia treatments are completed, in order to stimulate the immune system to cope with absorption of necrotic tumor tissue, to destroy any residual neoplastic cells and to prevent recurrence and metastases. Vaccine therapy can be administered on an ambulatory basis after the initial week or two, and the family physician can be trained to carry on maintenance therapy.

The Effect of MBV, Fever and Bacteria on Iron: More recently the *role of iron* has been recognized in the balance of host-parasite relations and some strains of virulent bacteria are known to acquire the capacity to sequester iron both in vitro and in vivo. [Iron: see above, Environmental Factors, page 29.] It has also been suggested that one of the beneficial effects of fever on the course of infection relates to the accompanying hyposideremia and consequent reduction in the availability of iron for bacterial cell growth.(884) *The possibility that iron, bacterial infection, fever and tumor regression are connected has not been sufficiently explored.*(229a; 613; 614) However, recent studies in vitro and in vivo have shown that tumor cells utilize iron in a fashion possibly similar

to bacteria(335) and also through surface receptors for the iron binding protein transferrin.(204;885)

The effective competition of bacteria for a nutrient indispensable for tumor cell growth could play an important role in the reported regressions of cancer associated with severe bacterial infections, or following aggressively administered MBV. In addition, recent work on the action of iron on a number of immunological functions tested in vitro(627;628;885) and on the immunological function of patients with iron overload, has shown that *both iron and ferritin have immunosuppressive effects on the macrophages and on T-lymphocyte function.*(884)

Thus, a fine balance seems to have evolved between bacterial infection, iron deficiency, fever, immune function and tumor cell growth. Therefore, when the incidence of infections is reduced, or the frequency of iron deficiency is decreased by use of iron-supplemented or iron-rich diets, or the immune system is partially suppressed by exposure to iron and other metals through occupational or environmental pollution, the balance may favor tumor development. These hitherto unrecognized factors may all have contributed to the increased incidence of cancers in developed countries observed in the past 90 years. In this period infections have been effectively eliminated or controlled and iron supplements have been widely used.

Mechanisms of Action of MBV: No one using MBV empirically during Coley's lifetime or until recently, knew that, in addition to producing fever, bacterial vaccines also stimulate the reticuloendothelial system, activate macrophages, increase hematopoiesis and increase production of prostacyclin, endogenous interferon and endorphins. We now recognize that these far reaching effects were responsible for causing regression of extensive tumors and preventing recurrence and/or metastasis. In addition, immediate pain relief, improved blood picture, appetite and weight gain and rapid wound healing and regeneration of bone occur in cases in which bone had been destroyed by the tumor or removed at surgery.

The mechanism of action of bacterial vaccines is extremely complex. Their effects are mediated through the interactions of macrophages, B and T lymphocytes, including subpopulations of cytotoxic helper and suppressor cells. The balance of these effects may be profoundly affected by the dose, timing and route of administration.(602–619)

Antigenicity: Braun and Kessel reported that the stimulatory effects of bacterial endotoxins on antibody synthesis and host resistance may be associated with the release of cell breakdown products from macrophages and other cells. They believed that stimulation of host resistance by endotoxin may involve the stimulation of specific antibody-forming cells by oligonucleotides in cell breakdown products that are released as the result of antigen-antibody reactions on cell surfaces. "Such rapid triggering of immune defenses . . . can occur only in cases where more than one exposure has been experienced. . ."(94a)

Several oncologists have shown that cancer patients respond best to microbial products to which they have previously been exposed. Staphylococcus and Pseudomonas aeruginosa are now the most frequently isolated organisms. Using these and others including Serratia marcescens, Waisbren has been successfully administering a mixed bacterial vaccine to prevent septicemia in critically burned immunosuppressed patients in a regional burn unit in Milwaukee, Wisconsin. Because of these results Waisbren has been treating his cancer patients with mixed vaccines with encouraging results.(866)

Coley and others using his MBV did not realize that streptococci *can increase the antigenicity* of plant polysaccharides such as agar, which are not antigenic, or of tumor cells which are weakly antigenic. Glynn and Holborrow showed that agar excites an

excellent immune response in rabbits when given as a vaccine adsorbed onto streptococci or staphylococci.(321) For this to occur it was essential that the organisms or their vaccines come into close contact with the target tissue. This underlines the importance of site of injection when using MBV.

MBV—Side Effects: No deleterious side effects have been reported with MBV therapy when correctly administered. Fever and chills occur but are regarded as beneficial as noted above. Patients should be informed of this. To increase the therapeutic effects of the fever patients should be wrapped in warm blankets during the reaction period.

Nausea and vomiting may occur if injections are given after meals. Some headache and malaise may be observed. Transient herpes labialis (cold sores) may occur after too large doses.

Corynebacterium parvum: In 1953 an anaerobic diphtheroid-like bacillus was isolated by Prévot from a case of septicemia.(6) He and Halpern reported that single or repeated injections of heat-killed C. parvum caused intense and prolonged stimulation of the phagocytic capacity of the reticuloendothelial system, accompanied by an increase in the weight of the liver and the spleen.(351) In 1966 Halpern reported the inhibition of tumor growth by killed C. parvum.(349)

At a conference chaired by Medawar on Immunopotentiation under the auspices of the Ciba Foundation, Halpern and his colleagues discussed the potent immunopotentiating effects of C. parvum in experimental infections and in malignancies. Treatment with killed C. parvum resulted in rejection or reduced growth rate of various experimental malignant tumors or leukemias in rodents. The effects were variable and depended on the nature of the tumors, the genotypic relation between the donor and the recipient, and *especially the strain of C. parvum and the route and timing of administration*.(350)

C. parvum appears to act at different cellular levels of the immune reaction: 1) it stimulates macrophages, increasing their phagocytic capacity and intracellular killing power towards ingested bacteria; 2) it stimulates the activity of T and B lymphocytes, increasing antibody synthesis against thymus dependent or thymus independent antigens; and 3) it potentiates delayed hypersensitivity and lymphocyte cytotoxic activity. The cytotoxic property of lymphocytes obtained from C. parvum-treated animals toward tumor cells is greatly increased. The cytotoxic action of lymphocytes of tumor-bearing animals against their own tumor cells is potentiated, but also that of lymphocytes from normal animals. The promising results obtained with C. parvum in human cancer stress the interest of this group of immunopotentiators in general and of C. parvum in particular.(351)

Clinical Trials of C. parvum: Israel has evaluated the effects of C. parvum clinically as well as experimentally beginning about 1967. By 1974 he had treated 414 patients of which all were evaluable for toxicity, 330 being in controlled or pilot studies. A report of his results was read at a symposium in Paris in May 1974. He recognized the vital importance of studying such factors as dosage, frequency and duration of these injections, as well as timing as related to chemotherapy or other modalities. He stressed that such immunotherapy should *not* be limited to cases with minimal residual disease, and that it should also be used *prior* to chemotherapy. Results obtained by immunotherapy alone, chemotherapy alone or immunochemotherapy combined should all be evaluated and end results compared. It may be that C. parvum alone is not potent enough, that chemotherapy alone is too immunosuppressive, and that a combination of the two agents may produce more adequate control of various types of tumors.(424)

C. parvum therapy protects the host from the immunosuppressive effects of chemotherapy but apparently cannot prevent the loss of immune competence due to the lesion itself in advanced cases.(424) Thus the tumor burden in such patients should be reduced by incomplete surgery or chemotherapy in order that adjuvants such as MBV or C. parvum may express their optimal activity.

For several years Israel used weekly injections of C. parvum given subcutaneously. Later he has used intraperitoneal injections given daily for as long as three months and he found they were very well tolerated.(424) To our knowledge only one patient ever received MBV intraperitoneally—a terminal ovarian carcinoma, with spectacular success.(610, Series B, Case 5, pp. 35–41.)

Israel reported that in metastatic breast cancer there has been more than a two fold difference in survival at twelve months and a fourfold difference at 18 months. One patient had a complete regression of massive liver metastases lasting more than two years and remained alive when reported in July 1974.

Beginning in January 1974 Israel began using daily intravenous injections of C. parvum alone in patients with disseminated disease. He concluded that the possibilities of C. parvum therapy and immunopotentiation in general are far from being fully explored. The optimal dose, frequency and duration of therapy are not yet known, nor which types of tumor may be most sensitive to such therapy. He added that it is now time for clinicians to answer these questions and to develop better methods of monitoring immunotherapy.(424)

Jones and Castro's studies show that the anti-metastatic effect of C. parvum appears to be mediated through macrophages in concert with a subpopulation of T lymphocytes, which were considered necessary in the sensitization arm of the response as opposed to the effector arm.(430)

Fisher and Gebhardt have reported on the effects of C. parvum alone or combined with cyclophosphamide (CY). They found that the combination was more effective than either one alone.(268)

Side Effects: C. parvum is not without side effects some of which may be deleterious.(318)

a) Fisher et al noted that nausea, vomiting, headache and confusion are not infrequent. This "flu-like" syndrome lasting 24 to 48 hours occurs after almost all courses of C. parvum.(273)

b) A febrile response and chills of considerable severity occur in almost all patients given intravenous injections of C. parvum, but these reactions are considered beneficial.

c) Site of injection as it effects reactions.

1) The subcutaneous route seems the least effective and can produce undesirable *local* reactions.(273)
2) Krahenbuhl el al showed that the intraperitoneal route was more efficient in activating macrophages than the intravenous route; they also found the subcutaneous route to be ineffective.(462)
3) The use of i.v. injections in patients with cerebral metastases may be hazardous.
4) Local injections of C. parvum into a metastatic lesion of malignant melanoma caused a temperature of 44°C. in the center of the lesion 24 hours later. (It had been 35°C. at the time of the injection.) This increased local heat at the site of melanoma lesions was observed following injections of MBV and sometimes revealed the presence of as yet undetected metastatic lesions.(293)
5) Intravascular coagulation: In rodents Lampert et al found that C. parvum induces intravascular coagulation lasting up to seven days. This results in thrombosis of hepatic

vessels with hepatic necrosis and thrombosis in pulmonary and splenic vessels.(470) This complication has not been reported with MBV.

6) *Increased sensitivity to anesthesia and barbiturates. C. parvum injections rendered mice lethally sensitive to normally safe anesthetic doses of tribromoethanol (avertin) and pentobarbitone (nembutol).*(589) All the mice died without recovering from the anesthetic when C. parvum had been given three to 13 days previously. C. parvum, irrespective of dose or time of injection, did not sensitize the mice to ether. Ether is mainly expelled through the lungs, and does not depend on the liver for breakdown, whereas the other two anesthetics are detoxified by the liver. Given i.v., C. parvum appears to interfere with this process. Lampert et al observed the abnormal sensitivity to barbituates following C. parvum. These findings suggest that caution should be exercised in using these compounds in patients receiving C. parvum or other bacterial vaccines intravenously.(589)

BCG Vaccine and Breast Cancer: Bacillus Calmette Guérin (BCG) is an attenuated strain of Mycobacterium bovis. It was developed at the Pasteur Institute in Lille, France in 1921 after 13 years' effort, and 231 serial passages from the original strain. It was grown in a culture medium containing beef bile as an emulsifying agent. Since its first clinical trial as a vaccine against tuberculosis in 1921, hundreds of millions of vaccinations have been performed, with very little morbidity.(41)

Almost 40 years elapsed between the isolation of BCG and its application for the control of cancer. In this period stimulation of the reticuloendothelial system had been associated with prevention of tumor growth, and BCG was found to be a potent reticuloendothelial stimulant.(639)

In the United States, Old et al were the first to report the beneficial effects of BCG on tumors of mice.(640) Since then a great many experimental studies have been made here and abroad, and BCG has been used to treat many types of cancer in man, principally malignant melanoma, but also breast cancer. In recent reports anergic patients have fared as well as those who are immunologically reactive in BCG-associated prolongation of tumor remission. Immunostimulation, and not merely inflammation, appears to be necessary to produce a BCG-induced antigenic effect. Kaledin et al suggested that patients predisposed to neoplastic disease should be vaccinated with BCG.(437)

Vaccine Preparation and Route of Administration: Chaparas and Hedrick compared 10 different viable preparations of BCG previously shown to be antigenically similar. It was found that they showed a broad range of immunostimulant potential and therapeutic effectiveness.(133) Zbar et al produced an antitumor effect with non-viable BCG extracts.(979)

Several studies have indicated the marked variation in potency of different strains of BCG, some of which seemed to be ineffective.(133;469) The Pasteur and Tice strains seem to be more effective than others. The best preparation for treatment of a given tumor, the optimum dose and the most suitable mode of administration have only recently become the subject of a randomized clinical investigation.(81)

The route of administration and dose, rarely stressed in earlier studies, may determine whether tumor suppression or enhancement is produced.(81) Some studies, such as that of Bast et al showed that potentiation of tumor growth may occur.(41)

Inadequate data concerning effective agents lead to their suboptimal use. Bluming believes that this is the greatest risk assumed by cancer immunotherapists today.(81)

Side Effects or Complications of BCG Immunotherapy: Bast's comprehensive review of BCG is the most complete.(41) He outlined the possibilities and limitations of BCG

for immunotherapy of cancer. The promise of this agent as a means of control is real, but so are the hazards associated with its use.(81)

Systemic reactions to BCG depend upon the route of administration, on the number of previous injections, and possibly upon the dose of BCG. After repeated intradermal or intratumoral injections, chills, fever and malaise have been observed. The febrile reaction occurs several hours after inoculation and persists from one to four days. Although the fever is often low grade, it may reach 40°C. Recurrent fever may develop three to four weeks after intralesional injection of BCG in association with a flu-like syndrome of nausea, pain in muscles and occasionally in joints. If untreated, symptoms usually subside in eight to nine weeks.(41)

Kaledin et al noted that when the number of mycobacteria injected was high, *tumor growth was stimulated* in mice. They concluded that high doses of BCG may be dangerous in human cancer immunotherapy.(437)

Bluming sounded a note of caution in 1972, noted that hepatic dysfunction occurred in 24% of patients injected *intralesionally* with BCG.(81)

In immunosuppressed patients persistent BCG infection has been observed in vaccination sites, in lymph nodes, in pleura and in a paraspinal abscess. Miliary caseating granulomas have been found at autopsy in patients who died from melanoma.(41)

Gerner and Moore noted that BCG produces ulcerating lesions at injection sites which are extremely painful and which take two to three months to heal.(315)

Bast cites other complications that have occurred, including severe hypersensitivity reactions, including anaphylaxis and a syndrome resembling tuberculin shock following repeated intralesional injection of BCG. Two patients have died following intralesional BCG injections.(41) Taken together the morbidity and mortality associated with intralesional injections of BCG are cause for concern. If survival is prolonged in a significant percentage of cases following injection of cutaneous metastases, the benefit obtained from BCG may outweigh the potential hazards.

Complications of BCG immunotherapy given orally or intradermally by scarification or by Heaf gun have been less frequent and less severe, with no fatalities among several hundred patients so treated. Unfortunately, there is no evidence to date that BCG administered by the less hazardous route can produce regression of intradermal tumor nodules.

The reader is referred to Bast's review for more detail.(41) He stated "with continued investigation BCG may well prove of value in certain clinical situations. From the data available at present, however, we cannot recommend BCG for use in general practice. Administration of BCG as a last resort seems particularly inappropriate. BCG-induced regression of clinically apparent visceral metastases has not been reported. From clinical and experimental observations, it seems that *BCG can accelerate the growth of tumors in patients with advanced disease*. Consequently we urge that the use of BCG in patients with cancer be limited to controlled clinical trials."(41)

BCG in Breast Cancer: Gutterman et al were the first to report on a series of disseminated breast cancer patients treated by a combination of chemotherapy, FAC, (5FU, adriamycin and cyclophosphamide) and BCG. The results were compared with FAC alone. The remission rates (73% and 76% for FAC and FAC-BCG respectively) were similar. However the duration of remission of the patients receiving BCG was longer. Thus 21 of the 34 patients achieving remission on FAC-BCG were alive at last follow up (median over 22 months) compared to 11 of 32 patients achieving remission on FAC (median 15 months.) The data suggested that further trials with BCG should be carried out on breast cancer patients.(341)

Staphylococcal Vaccines: As noted above, p. 36, and below in Part II, concurrent staphylococcal infections produced the largest number of complete and *permanent* regressions in cancer patients.(611)

It is now apparent that Staphylococcus aureus filtrates strongly activate the lymphocytes of most individuals. The degree of activation increases with the dose.(503) Two staphylococcal preparations used to increase host resistance in cancer patients are discussed here.

Staphage Lysate: Staphage Lysate (SPL), prepared by Delmont Laboratories, Swarthmore, PA has been used for over 30 years as a specific and useful therapeutic agent in the treatment and control of staphylococcal disease or asthma.(614) A few oncologists have used it as an adjuvant to other modalities in treating cancer.(614) SPL is administered intradermally, topically in or on the tumor area and by aerosol therapy. The nasal membranes permit the passage of many antigens. Absorption is fast—more rapid than oral administration and comparable to the intradermal route. This preparation can be helpful in preventing staphylococcal infections in immunosuppressed cancer patients.

Kim et al found that SPL is one of the most potent immune interferon inducers.(453) Aoki et al also reported that SPL is a strong inducer of interferon.(22)

Staphylococcus Protein A: Staphylococcus protein A is a constituent of the cell wall of Staphylococcus aureus which reacts with the Fc region of immunoglobulins from many mammalian species and combines with immune complexes in the serum. By extracorporeal perfusion over Staph. protein A this procedure nonspecifically removes blocking factors from the patient's plasma.

The first group to report their work with this technique was Bansal et al (1978) who observed improvement in the general condition of one colon carcinoma patient as well as a decrease in tumor size and histological changes consistent with tumor destruction.(37)

Ray and his colleagues in Philadelphia have further modified the immunoadsorption technique and extended their studies on three tumor models simultaneously, i.e. rat mammary adenocarcinoma,(690;693;694) canine vernereal tumors(689;691) and metastatic human colon carcinomas.(691;692) They reported tumor regressions in all these tumor models.

Ray et al have observed significant potentiation of anti-immune reactivity in the tumor bearing hosts. This treatment is associated with febrile reactions and shaking chills. Histologic evaluation of biopsied tumors showed fibrotic and necrotic reactions and lymphocytic infiltrations. Complement activation, decreased blocking activity, increased skin reactivity to recall antigens (delayed type hypersensitivity reactions), elevation of rosette forming cells, plasma-mediated potentiation of lymphoctyte cytotoxicity, and increased antitumor antibody activity were also reported by Ray et al as the consistent findings in their responding tumor bearing animals.

Ray and Bandyopadhyay have recently observed that cancer patients' plasma can elute several types of biomolecules from Staphylococcus aureus Cowans 1 during the *in vitro* adsorption procedure.(688) Also they have observed the eluted bacterial components can cause tumor necrosis in animals. Thus Ray believes that removal of blocking components from the plasma on the one hand and stimulation of immune reactivity of the host by the leached bacterial components on the other hand, may have contributed to the observed tumor regressions in rat, dog and human tumors.

Terman et al used this procedure in dogs with spontaneous mammary adenocarcinoma. A single nontoxic infusion of cytosine arabinoside was given after extracorporeal perfusion of plasma over immobilized protein A bearing S. aureus. This results in a necrotizing response rapid in onset and specific for tumor tissue. Gross tumoricidal reactions 12 hours

after this combined treatment exceeded the algebraic sum of responses to either agent given alone in the same dogs, implying a synergistic effect.(823)

Terman then extended this approach to patients with adenocarcinoma of the breast, with the initial objective of determining whether an anti-tumor effect could be demonstrated in large easily measurable lesions. Five consecutive such cases who had relapsed while under conventional therapy were given autologous plasma or plasma from similar patients which had been perfused over purified protein A immobilized in a collodion-charcoal matrix (PACC).(824) This was sometimes followed by intravenous cytosine arabinoside, 2 to mg/kg of body weight. These procedures were repeated and objective partial remission or improvement was observed in four of the five patients. They concluded that these preliminary results warranted further study of the mechanism involved in the antitumor effect as well as the potential value of the technique.

Another study at Memorial Sloan-Kettering Cancer Center by Jones et al (1980) concerns the treatment of feline lymphosarcoma, a rapidly fatal disease. Using this procedure, preliminary results show disease regression in 11 of 12 cats lasting up to three years. This is the first report of actual cure in this tumor as well as the first report of therapeutic clearance of a persistent viraemia by this procedure. (Personal communication, 1982.)

Bensinger et al treated five patients presenting with breast adenocarcinoma associated with metastases to bone or liver with plasma perfused over immobilized protein A. Three of the patients were otherwise completely untreated, and the other two received cytotoxic drugs until six weeks before immunoadsorption. Each patient was treated once or twice a week. During each procedure three litres of plasma were passed through the protein A column and returned to the patient.(54)

All five patients had mild hypotension and tachycardia and sometimes a fever during the procedure. They had pain at tumor sites immediately after the first treatment. The tumors decreased 25 to 50% in three patients after two, three and five treatments respectively. Bone pain was markedly reduced in one patient after the fourth procedure, and after six treatments bone radionuclide scans demonstrated a decrease in hyperactive areas. Histologic studies of two tumor-biopsy specimens showed necrotic cancer cells.(54)

Their results therefore confirm the data of Terman et al concerning the therapeutic effectiveness of ex vivo plasma perfusion over protein A in breast cancer patients. Unlike Terman, Bensinger et al did not provide additional therapy and they used 200 mg. of protein A covalently linked to silica gel instead of 5 mg. without the side effects Terman described. Bensinger concluded that the beneficial effects of such treatment may be related to the binding of IgG or of IgG associated with polypeptides (or both) to the immunoadsorbent.(54)

We believe that Ray and others should now evaluate the effects of intravenous injections of Staph A or Staphage Lysate (SPL) alone to see if most of the benefit is due to the Staph rather than to the removal of blocking factors by the more complicated perfusion procedure.

***Lactobacillus bulgaricus LB-51 (Anabol)*:** Bogdanov, of Sofia, Bulgaria has recently reported the beneficial effects of this preparation on 100 cancer patients.

Before these clinical studies could be undertaken in 1967, 2000 fractions of Lactobacillus bulgaricus were screened in 60,000 tumor-bearing mice (Crocker Sarcoma 180). At first Bogdanov believed the intravenous route was necessary, but subsequently he found that the oral preparation which he named Anabol, was entirely effective and much easier to use, as patients could continue the treatment daily at home for many months.

Bogdanov has recently reported on 100 cases so treated since 1967.(81a) The first group includes 45 cases of inoperable metastatic or terminal cancers in whom this was the only therapy. Complete regression occurred and patients were traced 1 to 14 years after onset of treatment.

Of these 100 cases six were metastatic breast cancers of which three received anabol alone with complete regression. (See below, Series 7, cases 1,2,3, p. 254) The other three received chemotherapy or radiation given "under anabol protection." These patients had little or no leukopenia and no nausea or other gastrointestinal side effects and the therapeutic response to chemotherapy appeared to be enhanced.(81a) (See Series 7, cases 4,5,6)

These findings not only in breast cancer suggest the importance of cooperative trials in Europe and the United States using anabol both to protect against the deleterious effects of chemotherapy and radiation but also to potentiate their therapeutic effects.

***Tumor Necrosis Factor (TNF)*:** Tumor Necrosis Factor (TNF) is a glycoprotein produced and released into the circulation following the combination of BCG sensitization and endotoxin challenge. This substance mimics the tumor necrotic action of endotoxin itself. BCG injected mice show a 23-fold increase in the lethal effects of endotoxin and a markedly enhanced ability to produce interferon following decreasing doses of endotoxin.(127) Not all strains of mice produce TNF. Their ability to do so seems to be linked to the ability of their RES to respond to the bacteria.

Several microorganisms have proved effective as *sensitizers*. These include BCG, Zymosan (derived from yeast), Corynebacterium parvum, and Corynebacterium granulosum. Old et al have found C. parvum (Burroughs Wellcome) the most consistently effective, BCG strains vary. Many gram negative bacteria may be used for endotoxin challenge. Old et al have found that Escherichia coli (Difco 0127B8) is the most effective.

A single injection (0.5cc) of TNF-positive mouse serum causes regression in approximately 20% of Meth A fibrosarcomas in mice. With multiple injections of smaller doses over a six week period up to 40% of the tumors regress. These effects are due to TNF not to residual endotoxin, as proven by limulus assay.(396)

Mouse TNF is cytotoxic or cytostatic to a wide variety of both human and mammalian tumor cells in tissue culture. It is nontoxic to normal cells in tissue culture. (Old et al, in press 1983.) It has not yet been used on patients in this country.

Rabbit TNF has been patented in Japan and clinical trials will begin there late in 1983. (Old, L. J., Personal Communication; 1983)

Williamson et al at Sloan-Kettering Institute, now have a human TNF produced from a B cell tumor line of human origin. This human factor has the same specificity against human tumor cells in tissue culture as mouse TNF. It also causes tumor necrosis of Meth A sarcoma in mice.(905a)

Old noted in 1981 that there had been a rather general feeling that the host has only a limited capacity at best to rid itself of naturally arising cancer cells. He added, "Our experience with TNF and the anti-leukemic factor in normal plasma has led us to realize that this attitude may greatly underestimate the body's potential for selective elimination of cancer cells."(638)

We believe that the cases cited in Part II, Series G, in whom inoperable very extensive ulcerated breast cancers "melted away" after "gangrene" developed, may have been the results of TNF. These astonishing results occurred in the early 19th century, before bacterial infections had been controlled.(611) Old's group proposed that TNF mediates endotoxin induced tumor necrosis and that it may be responsible for suppression of tumor cells by activated macrophages.(396)

Miscellaneous Microbial Immunomodifiers: *Brucella abortus*: An extract of Brucella abortus (Bru-Pel) is being studied by a number of investigators including Fisher and Gebhardt.(268) Glasgow et al believe it shares a number of characteristics with recognized immunomodulating agents. One mechanism which it modulates through activation of macrophages is host resistance to tumors, to viral infections and to challenge with Listeria monocytogenes.(319)

Chirigos et al found that if *Brucella abortus* (strain 456 ether extract) was administered with L1210 irradiated tumor cell vaccine, antitumor activity was maximally expressed when vaccine and adjuvant were administered by intraperitoneal injection. They also found that pyran co-polymer and glucan were equally effective.(136)

Coliform Vaccine: Compton, a British bacteriologist, Director of Laboratories in Alexandria, Egypt first used a salmonella-coliform-giumaiform phage preparation for the treatment of an intestinal upset in a patient suffering from cancer of the liver. The patient insisted that it relieved the symptoms of his cancer and therefore continued it for several months. This observation led Compton to try the same phage preparation in a case of an English physician aged 45 who was suffering from breast cancer metastatic to the left ilium with beginning pathologic fracture. Lesions were also present in the lumbar vertebrae and 12th rib. She was in severe pain and bedridden when Compton began using the lysate. Ampoules were given orally half an hour before meals. Pain relief occurred immediately so morphine and aspirin were no longer needed. Two months later she left Alexandria by boat for England, in apparent remission. (This was April 1945 and due to the war she had to go around Africa.) Unfortunately the supply of lysate gave out on the voyage, and the disease reactivated when she got to England.(166a) (See below, Part III, Series 6, p. 252 for more detail.)

These cases led Compton to study the effect of ingestion of irradiated Escherichia coli in mice bearing transplanted tumors. Three different coliform bacilli irradiated at 15,000 to 30,000r were used, causing retardation of growth in 60% of the mice, while 100% of the controls grew without interruption.(166b) These anecdotal findings suggest that ingestion of bacteria in water and milk 80–100 years ago in Western countries may have been somewhat protective in inhibiting incipient cancers from becoming clinically apparent or in lessening the incidence of recurrence or metastases following surgery.

Bordetella pertussis: Likhite recently studied the effect of killed Bordetella pertussis organisms admixed with mammary adenocarcinoma cells prior to inoculation. This caused rapid and permanent rejection that began two weeks after inoculation. Histological sections of regressing tumors revealed infiltration of macrophages, lymphocytes and numerous mast cells.(501)

Polidin: Polidin is a heat killed suspension prepared from Streptococcus pyogenes, Streptococcus viridans, Neisseria catarrhalis, Diplococcus pneumoniae, Eschercchia coli, Klebsiella pneumoniae, Streptococcus faecalis, Staphylococcus aureus, produced by Dr. I. Cantacuzino Institute, Bucharest, Roumania.

Kiricuta et al are the only investigators we have found who have used both immunotherapy with a mixed bacterial vaccine (Polidin) and an anticoagulant (heparin), in order to decrease the incidence of metastases.(455) They used 400 mice divided into four groups: I. Controls; Group II received Polidin injections begun a month prior to tumor inoculation, and continued for two months afterward twice weekly; III. Heparin alone, the first dose, 100 U intravenously just prior to tumor cell inoculation, and starting with the second day, 100 U intramuscularly every 48 hours for 10 days; IV. Heparin and Polidin.

The results showed that in Group II, Polidin markedly extended the latent period before metastases developed, without significantly modifying the ultimate incidence of metas-

tases. In the Group IV in which both immunotherapy and the anticoagulant was used there was a marked decrease in the incidence of metastases (28%) compared to Group II, Polidin alone, (76%), or Group III, heparin alone, (47%). The untreated controls had an incidence of 83%.(455)

Comparative Effects of Various Immunotherapeutic Agents on Breast Cancer in Mice: Unfortunately there have been very few studies of the comparative efficacy of various immune stimulants either in experimental or human breast cancers. Therefore the study of Purnell et al is important.(685) They used C. parvum, Bordetella pertussis, BCG and levamisole alone or combined with cyclophosphamide (CY) in the CAD2 murine mammary adenocarcinoma system. Weekly systemic intraperitoneal injections of C. parvum, B. pertussis or BCG were effective in controlling tumor growth and had equivalent antitumor effects. Weekly treatment, or a single injection of levamisole was ineffective. However, a single injection of C. parvum or BCG was as effective as weekly systemic treatment. When given as a single injection, C. parvum and BCG were superior to B. pertussis in controlling tumor growth. Effects on period of survival following systemic administration of immune stimulants were not always correlated with effects on tumor size. BCG and CY given together were significantly more effective than CY alone.

Fisher and Gebhardt also evaluated several other nonspecific immuno-stimulating agents (NSSAs): Brucella abortus extract (Bru-Pel; BP) and glucan (GL) as well as BCG, tilarone and levamisole.(268) None of these agents inhibited the murine mammary tumor when administered systemically without CY. Whereas tumor regression was observed following intratumoral CP, neither GL nor BP had such an effect. When used with CY neither BP nor GL given intraperitoneally or intratumorally inhibited tumor growth as effectively as did CP and CY. Inhibition of growth of a distant tumor as well as the treated tumor occurred following intratumoral CP and CY but not after intratumoral BP and CY. All the microbial NSSAs increased macrophage colony production to varying degrees in both normal and tumor-bearing mice. In the latter CP had the most prolonged effect. Levamisole and tilerone failed to increase colony production in normal mice while in tumor-bearing mice the effect was inversely proportional to the amount administered.(268)

Fibrinolytic or Proteolytic Bacterial Enzymes: Bacterial enzymes have elicited interest as possible useful adjuvants to cancer therapy. These include those produced by streptococci, *streptodornase* and *streptokinase* which undoubtedly played a role in the regressions occurring after concurrent erysipelas or other streptococcal infections.(611–614) Tillett observed that the effective clearing of the site of infections (or tumors) through enzymatic action, renders the area permeable to humoral and cellular forces of both natural and specifically acquired immunity. As a result of Tillett's work *Varidase* was developed from streptodornase and streptokinase.

Another inportant enzyme is *neuraminidase*. This is derived from the influenza virus and from Vibrio cholerae filtrates. Neuraminidase removes sialic acid residues on the tumor cell surfaces. It causes a marked decrease in viscosity and concomitant loss of biological activity of this glycoprotein. Removing these residues may remove stearic hindrance to antigen perception, reduce the negative charge of the cell, increase cell deformability and increase the susceptible cell to phagocytosis.(755; 888) Thus, neuraminidase treatment of tumor cells leads to increasing their antigenicity.

It has been used experimentally by a number of investigators including Simmons and Rios. They found injections of Vibrio cholerae neuraminidase causes regression of spontaneous mammary carcinomas in mice. Simmons and Rios also produced the total immunospecific regression of firmly established MCA fibrosarcomas in mice by inoculation of living tumor cells heated in vitro with Vibrio cholerae neuraminidase plus mitomycin

C. By comparison BCG injected directly into the tumor nodule or subcutaneously at distant sites reduced the growth rate but rarely induced complete regression. The maximum effect was obtained by combining neuraminidase-treated tumor cells with injection of BCG at the same site.(755)

As stated above both Varidase and neuraminidase appear to decrease viscosity, therefore these proteolytic enzymes may prove useful in the treatment of human breast cancer, especially those which produce mucin.

Yeast Extracts: The first studies on murine tumors were those of Lewisohn et al beginning in 1940 using intravenous injections of an aqueous extract of brewers yeast. This caused regression of spontaneous mammary adenocarcinoma in mice. The addition of either pantothenic acid or riboflavin to the yeast extract appeared to improve the effectiveness of the latter in preventing the development of transplanted and spontaneous tumors.(494; 495)

The use of pure cultures of bakers yeast inoculated in 60 cancer patients about 1896, produced 18 cures, some of several years duration. Of these four had recurred following surgery. This procedure caused leukocytosis.(540) Maisin et al reported the effect of heat-treated bakers yeast on development of benzpyrene-induced tumors in mice. Only 1.2% of the yeast-fed group developed cancers, as compared to 23.2% of the controls.(539)

In 1958 Smith et al reported on the protective effects of zymosan on irradiation mortality. In general the increase in resistance paralleled the ability to mobilize granulocytes. Intraperitoneal injection of zymosan also increases resistance to infection without producing granulocytosis. The rapidly developing resistance to infection is transitory (one to two days.) These authors attribute the fact that endotoxin induces earlier hematopoietic recovery as being responsible for increase in survival after irradiation, rather than to the temporary increase in resistance to infection.(769)

In 1964 Martin et al found that zymosan when combined with cyclophosphamide and enucleating surgery in treating a spontaneous mammary cancer in mice significantly enhanced the therapeutic effect. Their data revealed the critical relationship between the dose of zymosan and the time of its administration.(549)

DiLuzio and his associates have studied glucan very extensively in recent years in animal tumors as well as clinically.(217;540) Glucan was given in doses up to 400 mg. intralesionally in patients with metastatic malignant melanoma and breast carcinoma and in inoperable adenocarcinoma of the lung. The response was dose dependent. With appropriate doses complete and lasting regressions occurred.(540)

Currently, further clinical studies are being carried out with intralesional glucan under Krementz at Tulane University. This study is confirming the earlier work of Mansell. (Personal communication from DiLuzio, 1981.) DeLuzio is now working on production of a soluble preparation of glucan which can be given intravenously.

Thus for about 35 years purified yeast extracts, such as zymosan, glucan and hydroglucan have been used to stimulate host resistance to cancer. Glucan effectively activates macrophages.(217) It also protects against bacterial infections.

Immunotherapy, Specific

Anderson et al reported the unexpectedly long survival among 16 breast cancer patients who were given autografts of irradiated cancer cells immediately after simple mastectomy and before postoperative radiotherapy.(20) Twleve of these were Stage II and four were Stage III. The poor prognostic features included tumors exceeding 4 cm., fixation to the

skin or fascia or axillary lymph node metastases. At six years 63% had survived as compared to 30% in the control group not receiving immunotherapy. They concluded that this high survival rate and the abnormally high cancer-directed reactivity of the patients' leukocytes in the migration inhibition test, indicate that a single irradiated autograft of mammary cancer may sensitize the residual tumor to subsequent conventional radiotherapy and in the process may activate systemic immunological restraints.(20)

Physiological Immunomodifiers

Interferon: Interferons, discovered by Isaacs in 1957 are a family of inducible glycoproteins produced by a wide range of vertebrate cells in response to viral infections as well as to a variety of other stimuli.(463;611) Ho et al were among the first to find that interferon can be induced by other substances besides viruses, for instance bacterial endotoxins. Other inducers include synthetic polymers resembling RNA (Poly I:C) and certain plastics such as pyran copolymers as well as statocolon, a double stranded RNA that comes from the penicillium mycophage.

Interferons have shown inhibitory effects on a wide range of animal tumors, and recent clinical trials have also demonstrated antitumor effects in man.(463)

In 1981 some batches of interferon were found to be weak and ineffective, and this was discussed in a television program resulting in a considerable negative reaction on the part of laymen to interferon research. This problem has now been resolved.

The effect of interferons on immune defenses is not completely understood. Interferons increase the expression of cell surface antigens. This may render tumor cells more susceptible to recognition and elimination by the host.(463)

Interferons have been shown to affect the specialized function of some cells involved in immune reactions. Thus, under appropriate circumstances interferons have been known to increase or decrease antibody responses, to decrease the proliferative response of lymphocytes to mitogens and alloantigens, to decrease or in some cases to increase delayed hypersensitivity reactions, to delay or accelerate graft rejection, to enhance macrophage phagocytic activity, and macrophage mediated tumor cell cytotoxicity, and to increase both specific and spontaneous cell mediated cytotoxicity.(463) They apparently enhance normal killer cell activity and by acting on T cells may modulate immune responses.

Singer et al studied the effects of a number of commercially available bacterial vaccines and allergenic extracts as regards induction of interferon in mice. They found that interferon was detected when the intravenous route was used and in certain instances after subcutaneous administration. The time of appearance and duration of interferon production were similar to those reported for endotoxin.(760)

Possible Role of Interferon in Breast Cancer Therapy: Thus far there have been very few clinical trials of interferon for breast cancer. Gutterman et al reported regression in seven of 17 advanced breast cancer patients receiving a remission induction schedule of 3 to 9 million antiviral units daily intramuscularly for 4 to 26 weeks. Toxicity included low grade fever, fatigue, anorexia and partial alopecia. Myelosuppression (lowest mean leukocyte count, 2,500/mm.) occurred in most patients.(340) Borden et al, reporting on the American Cancer Society sponsored cooperative trial, noted that five of 23 cases showed major objective tumor regression.(91) In neither of these studies was there evidence that higher doses of interferon (9×10^6 u/day) were more effective than lower ones (3×10^6 u/day.)

In Gutterman's study, response to interferon was positively correlated with response to prior chemotherapy or hormonal therapy, and was seen only in patients who developed at least moderate leukopenia, suggesting that interferon's inhibition of DNA synthesis may have played an important role.(340)

In planning interferon therapy for breast cancer patients now and in the future we must recognize which factors may augment circulating levels of interferon. Siegel noted that administration of ascorbic acid to mice in their drinking water caused augmented levels of circulating interferon after stimulation with murine leukemia virus.(750) In another study they found enhancement of interferon production by poly I:C in mice fed ascorbate supplemented diets.(751)

Among the factors shown to inhibit the synthesis and activity of interferon are stress, steroids, antimetabolites and carcinogens.(258) Thus the stress of trauma or surgery, or of chemotherapy and various forms of psychic stress, through their stimulation of endogenous adrenal corticoids, may have a deleterious effect on interferon synthesis.(751)

It is very important to remember that the same stimuli that result in interferon induction also induce the release of a wide variety of factors (e.g. lymphokines, monokines, prostaglandins) which are present in varying amounts in interferon preparations and which exert a variety of effects on cells. These factors may have been instrumental in both the toxicity of interferon preparations and in their therapeutic activity, or lack of it.(463)

As yet we do not know the optimal dose, frequency or duration of interferon therapy. If interferon's effects on immune responses are the most important factor, we need to explore which immune responses are involved in mediating tumor regression in man and to what degree they ought to be modified. The use of immunosuppressive agents that inhibit the release of endogenous interferon, such as corticosteriods, should be avoided.

Interferon may prove most useful in treating breast cancer as an adjuvant to surgery where the tumor burden is minimal. It may also prove useful in the inoperable cases combined with chemotherapy or bacterial vaccines.

***Effects of Bacterial Vaccines on Interferon Production*:** Oncologists using *exogenous* interferon may also wish to reinforce its effectivensss by using bacterial vaccines, since they have been shown to stimulate the production or release of *endogenous* interferon. Matsubana et al reported that Picibanil (a Japanese streptococcal preparation) induced twice as much interferon as levamisole and much more than lentinan or Corynebacterium liquifacines.(553) Singer et al reported on the induction of interferon by various American bacterial vaccines.(760) Stinebring and Youngner reported that endotoxin from Brucella abortus, E. coli, Salmonella typhimurium and Serratia marcescens all induce interferon production; these agents are rapidly sequestered in the cells of the RES.(795) They showed that BCG increases the reactivity of mice to endotoxin when measured by interferon response as well as by lethality.

***Lymphokines*:** Lymphokines are biologically active materials produced and excreted by lymphocytes and possibly by other blood cells, including macrophages. They are involved in practically every stage of the complex mechanism of the cellular immune response.(773) The work lymphokine was first proposed by Dumonde in 1969 and was initially applied to a factor produced by lymphocytes which inhibited migration of macrophages (MIF). This led rapidly to the discovery of a host of materials of lymphocytic origin which possessed a wide range of effects on macrophages, other lymphocytes and on inflammatory cells in general. In fact the term lymphokines was expanded to include a large number of substances or activities of unidentified materials which affect not only

the regulation of the immune mechanism but also of cell growth, and of vascular properties. The best known lymphokines include the skin reactive factor (SRF), the lymphotoxic factor and the migration inhibitory factors (MIF). Over 30 other activities affecting all aspects of the immune and inflammatory mechanisms have also been described. Interferon, transfer factor and thymosin are in fact also lymphokines according to the very definition of this term.

The possible relevance of lymphokines to the defective immune response associated with cancer in vivo was considered very early. The first indication of response of human cancer to lymphokines was obtained when a crude preparation of MIF, from human origin, was injected directly into accessible lesions of patients with metastatic breast cancer, first used by Djerassi in 1973 and cited by Papermaster in 1974.(612) These effects were soon reproduced with a mixture of lymphokines produced by a cell line of human lymphocytes.(612) Systemic administration to cancer patients of this mixture of lymphokines was first reported by Joshua and Djerassi.(432) A marked increase in the number of circulating T-lymphocytes and of the graft versus host (GVH) assay in rats of the patient's lymphocytes was observed within three hours after subcutaneous or intravenous injections of the lymphokines. A moderate, but prompt and very consistent shrinkage of cutaneous or subcutaneous cancer masses in these patients was also observed.(221;432)

Remarkably, the clinical effect of lymphokines on skin and subcutaneous lesions is fully developed in one or two days but cannot be enhanced further by continuation of the treatment. Lack of further tumor reduction may be due to exhausting the macrophage complement inside the tumor mass and the failure, or inability, of other macrophages to enter the lesion. On the other hand, lymphokines seem to be synergistic with chemotherapy in animals and possibly in patients. Combining lymphokines with effective chemotherapeutic agents may be the only reason for clinical use of these fascinating materials at this time.

Transfer Factor: Transfer factor is a low molecular weight dialyzable extract of immune lymphocytes which transfers cellular immunity from one individual to another and it does not induce the synthesis of blocking antibody. It was first described by Lawrence in 1955 who was able to transmit the sensitivity to specific antigens from sensitized to non-sensitized animals by the administration of lymphocytes from the former.(476) Eventually, a peptide material was associated with the transmission of antigen recognition in animals as well as humans.

A common confusion about the potential of transfer factor in the treatment of malignancies is that the transfer of specific immunity against the tumor is neglected and instead the transfer factor is used as a non-specific stimulant of immunity in general. The transfer of sensitivity to common and widespread antigens such as PPD, Candida, or bacterial antigens is expected in some mysterious way to be beneficial without actually stimulating the patients with the antigens themselves. Even the value of transferring sensitivity to the specific cancer antigens can be questioned on rational analysis. After all, the patient with cancer *is* sensitized to his own tumor well enough to produce the antibodies and the immune complexes which in fact may be the actual blocking factor protecting the tumor from his own cellular immune defenses.

Recently, transfer factor was proposed for the immunotherapy of patients with a number of different malignancies. An example of the studies on transfer factor is the work of Fudenberg and of Swedish investigators who used transfer factor obtained from the lymphocytes of relatives of patients with osteogenic sarcoma for the actual treatment of patients with this disease.(491) While no definitive effects on established disease were

observed, the preliminary studies seemed to suggest that the administration of transfer factor to such patients may delay or prevent the recurrence of disease following surgery. Studies of transfer factor in breast cancer and in other malignancies followed, with less than impressive results.

Synthetic Immunological Modifiers

Poly A:U: The double stranded Polyadenylic Polyuridylic acid known as Poly A:U has a fairly rapid rate of depolymerization *in vivo*. It has been preferred to the more slowly degraded Poly I:C, which possesses equal or even better immunoenhancing activity. Poly A:U is stimulatory without being toxic or pyrogenic. It stimulates phagocytosis, antibody formation, cell-mediated immunity and lymphocyte transformation. It also increases host resistance to a number of syngeneic tumors in mice and elicits high levels of antibody in certain types of genetic low responders.

In France, Jean and Fanny Lacour have conducted a randomized trial of Poly A:U on 300 breast cancer patients. They all had received the same treatment, simple mastectomy and radiation. The control group received saline placebos, the other group were given intravenous injections of 30 mg. Poly A:U per week for six weeks.(465–468) By 1980 140 in the control group and 145 in the treated group were evaluable. It was found that the four-year relapse-free survival rate was 77% in the treated group compared to 57% in the controls.

Levamisole: Levamisole is a veterinary antihelmintic (pet-worming) drug which in 1972 began to be studied for its effect on the immune system of cancer patients. Most of these were lung cancers. It is unclear as to how levamisole may modulate the immune system. The limiting toxic effect noted by several investigators was intractable nausea.(391)

Hershaut et al in New York carried out a randomized study of levamisole in breast cancer patients. This revealed no difference in survival between those receiving chemotherapy plus levamisole and those on chemotherapy alone.(391)

The Danish Breast Cancer Cooperative group reported *more* recurrences in patients receiving levamisole in addition to radiation than in those given postoperative radiation alone. The levamisole group experienced an unprecedented frequency of side effects especially in the postmenopausal women.(21)

Several oncologists have expressed concern about the high frequency of agranulocytosis among breast cancer patients receiving levamisole.(820) The alarming frequency of side effects observed in a levamisole treated group as compared to controls receiving placebo forced Retsas et al to suspend their trial after eight months.(698)

Specific Immunotherapy

A number of investigators have been using active specific immunotherapy for certain types of cancer, especially malignant melanoma and lung cancer. Tumor cells were admixed with bacterial vaccines such as BCG or C. parvum. The most important immunogens in these studies were the tumor cells but the host response was enhanced by the bacterial agent in the vaccine. Soluble tumor antigen preparations are usually ineffective due to preferential induction of suppressor lymphocyte responses. Removal of suppressor precursors by cyclophosphamide treatment of animals leads to the development of antitumor immunity following immunization with soluble antigen preparations. One

component of the immune response involves the generation of non-specific effector cells. This type of response can be induced by administering chemical hypersensitization agents so as to localize in tumor deposits and make them more strongly antigenic. Intralesional injections of alkylcatechols, the active constituents of poison ivy/oak (urushiol oil) localize in tumor cell membranes. These compounds are highly potent hypersensitizers.(34)

A large scale trial of active specific immunotherapy with tumor cell vaccines has been undertaken on breast cancer patients recently by a group in Israel. Unfortunately the results of this study are not yet available. We believe, however, that by injecting bacterial vaccines such as MBV with or without local injections of a hypersensitizer, it is possible to achieve significant immune stimulation. A study of cases of inoperable breast cancer receiving MBV suggest this is true. (See Part III of this book.) It is time that large scale cooperative breast trials be initiated on this type of immunotherapy.

NUTRITION FOR BREAST CANCER PATIENTS

Nutrition is an enormously complicated problem. On the one hand we must prevent anorexia and weight loss, on the other hand we must remember that tumor growth is slowed by starvation and that intravenous nutrition and iron supplementation increase tumor growth.(785)

The provision of optimal nutritional care requires a multidisciplinary approach with physicians, nurses, dieticians and pharmacists working as a team. Shils has outlined the principles of nutritional therapy for cancer patients which should be studied by oncologists.(746) This section deals with various aspects of nutrition for patients who have breast cancer. These include avoidance of dietary fat and reduction of weight, anorexia, hyperalimentation, iron, nutritional supplements and finally nutrition as it may affect chemotherapy, radiation, immunotherapy or recovery from surgery.

Dietary Fat and Body Weight: Donegan et al suggest that diet and weight reduction may improve the prognosis of heavy individuals with early breast cancer. They found a definite association between high preoperative body weight and both survival and risk of treatment failure after potentially curative surgery.(223)

The Fishers noted that a high fat choline-free diet caused an increased incidence of metastases in rats, but when they were fed choline no such increase occurred. They concluded that since nutritional factors seem to affect the course of metastatic development, the clinician must give them careful consideration.(364)

As noted above on pp. 25 and 30, both epidemiologic and laboratory investigations have placed dietary fat and obesity under increasing scrutiny as risk factors for the *development* of breast cancer.(219; 330)

Tartter et al '81 analyzed the disease free survival rates in 374 women with operable breast cancer.(818) They found that high preoperative weight, particularly in combination with high serum cholesterol was associated with an extremely poor cumulative five-year disease free survival, (32%) compared with that observed in women in whom values of either or both variables were low (68%). These findings indicate that weight and cholesterol, in addition to their previously reported effect on the risk of breast cancer development, significantly influence the subsequent course of the disease.(818)

Anorexia: Anorexia, inanition and weight loss are frequently the first manifestations of cancer. Much of the weight loss is from muscle wasting; this causes fatigue, weakness and inactivity.(215)

When the patient realizes she *has* breast cancer, a sense of hopelessness may develop leading to an adaptive biological reaction called conservation withdrawal. Schmale proposed that at times anorexia, inanition and weight loss are somatic consequences of the patient's beliefs and attitudes about her disease and its treatment. How this reaction is initiated and mediated biologically and how it may be related to and be reversed by a shift in motivation are questions of great importance.(737)

Hyperalimentation: Hyperalimentation, is now widely used for terminal cancer patients or briefly after major surgery. However, a concern has been raised that increased caloric intake may increase the tumor growth rate in man. The amino acid content of the diet seems to be the nutritional stimulus for tumor growth, independent of nutritional status. One should therefore use only a brief period of hyperalimentation after which oral caloric intake may be adequate.(785)

Nutrition During Breast Cancer Therapy: The nutritional consequences of major chemotherapy, radiotherapy, some forms of immunotherapy, surgery and anesthesia often unavoidably produce a variety of side effects such as nausea, vomiting, oral pain, diarrhea, fever or chills. These symptoms cause a further decrease in appetite, physical activity and body weight and these effects may leave a patient with a profound nutritional deficiency.

Most of the complications are reversible and resolve in a matter of weeks. The risks are small when compared to the natural conseqeunces of untreated cancer. Many nutritionally important untoward effects can be prevented or treated nonspecifically with antiemetics, analgesics, antidiarrheal agents, and transfusions of blood components during the initial critical phase of chemotherapy so as to maintain an appropriate nutritional status.(635)

When patients are placed on an elemental diet rich in calories, amino acids and vitamins before and during treatment with 5-FU and, in some cases, radiotherapy, they showed no drug related rectal lesions and maintained their pre-treatment body weight.(93)

Ohnuma and Holland believe that further treatment with chemotherapy is justified only when the patient can recover from its consequences. Otherwise the vicious circle of cachexia produced by the tumor and these toxic agents will not end, even if the tumor is apparently regressing. It is important to weigh the risks of treatment versus the possible benefits.(635)

Chemotherapy in combination with parenteral nutrition is well tolerated in cancer patients who are nutritionally depleted and who would otherwise be deprived of adequate chemotherapy for fear of complications from malnutrition and inanition.(635) Nutritionally less deprived patients are more likely to respond to chemotherapy.(475)

In experimental systems and in man evidence is accumulating which indicates that intermittent intensive chemotherapy is superior to continuous treatment. These findings should lead to short term intensive combined modalities to attempt tumor debulking, remission induction or cure, rather than using long continuous treatment which requires nutritional maintenance.

When chemotherapy is given as an adjuvant for breast cancer, the patients are ambulatory and maintain normal activity, and thus have normal appetite and nutrition. Chemotherapy thus produces minimal nutritional consequences.(635)

Vitamins: *Vitamin A.* Recently several European Clinics have used megadoses of Vitamin A in cancer patients. Vautier in 1813, advocated carrot juice as the only beverage for his patients and also compresses of scraped carrots mixed with conium for breast cancers.(858)

Cameron and Pauling have reported at length on the beneficial effects of *Vitamin C* in cancer patients especially as regards control or relief of severe pain.(120) They have also observed increased survival in advanced cancer patients, but not in those who had had prolonged chemotherapy first. The fact that other controlled studies have not as yet duplicated their results is attributed to the fact that the great majority of these cases *had* received a good deal of chemotherapy first.

Prasad noted that Vitamin C can increase the cell killing effects of certain tumor therapeutic agents and may stimulate the patient's immune system against residual tumor cells.(677) Further study on those effects must be done, using animal tumor models before assaying its role in the management of human neoplasms.

Siegel et al noted that administration of ascorbic acid to mice in their drinking water augmented levels of circulating interferon after stimulation with murine leukemia virus. In another study they found enhancement of interferon production by Poly I:C in mice fed ascorbate supplemented diets.(750)

Cancer patients may require *Vitamin E* during certain forms of chemotherapy to reduce toxicity. This vitamin is beneficial in fibrocystic disease of the breast: 600 units daily produced a clinical response rate of 85%.(3; 510; 774)

Eisman et al have shown that malignant and benign human breast tumors as well as rabbit breast tissue contain classical high affinity low capacity receptors for 1,25-dihydroxy *Vitamin* D_3. They believe this vitamin may activate calcium transport in the malignant as well as the lactating breast and may play a role in the development of bone metastases which occur in 80% of breast cancer patients with advanced disease. They raise the possibility that an effective antagonist might conceivably modify the course of the disease.(241)

Trace Elements: We have discussed the effect of *iron* on tumors above, pp. 28–29. It deserves serious consideration because too many women are being given iron unnecessarily and this may benefit the tumor to the detriment of the patient.

Zinc is essential to the proper rate of function of at least 70 enzymes in both animals and humans, and is obligatory in at least 35 of these including DNA and RNA polymerase, and thymidine kinase.(326) These enzymes, indispensable to DNA and RNA synthesis, play a critical role in both cellular and humoral immunologic responses, which depend greatly on rapid proliferation of immunocompetent lymphocytes and protein synthesis by these cellular elements. Good et al observed that zinc can function as a mitogen for lymphocytes in both animals and humans. Their studies have suggested that the development and expression of cancer may be influenced by the content of zinc in the diet.(326)

Zinc deficiency can reversibly halt tumor growth in a number of systems and may do so rapidly. Possibly dietary zinc deficiency may be used to halt the tumor cell cycle in adults, (not in children) to make cells more responsive to various therapies. However, zinc is required for the operation of the cellular immune response, which may be critical for successful host contribution to tumor cell kill during therapy. Thus, on this ground alone, proper nutrition in general, and zinc in particular, are critical for cancer patients. (Petering, personal communication, 1982.)

Schrauzer et al have studied the cancer protecting effect of *selenium*. They found that this is apparently counteracted by selenium-antagonistic elements such as zinc.(740)

Lymphocyte mediated cytotoxicity of tumor cells requires the establishment of a firm adhesion between lymphocyte and tumor cell. This occurs most efficiently in the presence of *magnesium* but may also occur with *calcium*. Frazier's experiments have shown the importance of dietary magnesium and calcium and Vitamin C in increasing the survival of mice with breast cancer, explained perhaps by promoting optimum function of the immune system with the provision of an adequate amount of cation for lymphocytolysis of tumor cells.(300)

Conclusions: It is clear that proper nutritional support is an essential factor in the multidisciplinary care of the breast cancer patient. This is not always easy during hospitalization, but dieticians are becoming increasingly aware that food should be both appetizing and nutritious. More effort is being made to include whole grain breads and cereals, fresh fruits, raw vegetables and salads and fish or poultry instead of beef, pork and sweet desserts.

De Waard stated in 1979: "If we are right in believing that 'western' diet and/or nutritional status contain promoting factors for breast cancer, then a few clinical nutritional trials could bring us another step forward. Weight reduction could alter prognosis in postmenopausal but not in premenopausal obese women. Such adjuvant therapy would be an elegant alternative to the regimens of combination chemotherapy that do not seem to be very successful in postmenopausal women."(209)

MANAGEMENT OF PAIN IN BREAST CANCER PATIENTS

Breast cancer rarely causes pain in the early stages. In this section we discuss the problem of pain resulting a) from treatment procedures or b) from metastases.

a) Pain from treatment procedures includes postoperative pain—the more radical the procedure the greater the pain; brachial plexus nerve entrapments and carpal tunnel syndrome; neuromas; pulmonary fibrosis resulting from radiation; b) pain arising from advanced disease, including metastases. This includes pain due to compression of nerve endings, pathological fractures, infiltration and obstruction of a viscus, inflammatory changes or necrosis.

The oncologist must do what is possible for the neoplastic lesions while working on pain control. Methods used include surgical procedures, administration of anesthesia, drugs, bacterial vaccines, vitamin C, acupuncture, psychological management, also pain control clinics and hospices for terminal patients.

Standard surgical procedures include a) immobilization of fractures due to bone metastases, b) relief of obstruction, c) drainage of abscesses, ascites or pleural effusions.

Neurosurgical procedures include a) neurectomy—cutting of the pain impulse, b) cordotomy—injecting or severing portions of nerves to the spine or brain. The neurological approach has drawbacks: paralysis, loss of sphincter control or morbidity. The patient may no longer accept surgery at this stage of her disease.

Anesthesia: Instead of exposing the nerve a needle is inserted near or in the nerve. Localization is not always easy. The effect of procaine is usually too brief and not worth the effort if it only lasts a few hours. Complications may occur such as numbness or paralysis. Strangely numbness is sometimes not tolerated as well as pain.

Drugs: It is important that the least potent drugs should be tried first, to delay using narcotics as long as possible so as to avoid addiction and side effects, including respiratory

effects. If one uses tranquilizers, hypnotics, muscle relaxants and antihistamines with narcotics, one can use much smaller narcotic dosage. Phenol and alcohol injected into nerves will produce neurological changes so that nerves will not work. The sensory, not the motor nerves must be injected. L-dopa provides prolonged relief from the bone pain caused by metastatic breast cancer. Minton found that administration of L-dopa is an easy way to predict a clinical response in such patients to subsequent endocrine ablation.(574)

Bacterial Vaccines: Injections of MBV (formerly known as Coley's Mixed Toxins) have produced marked pain relief in breast cancer patients, as well as regression of inoperable or metastatic lesions. (See Part III.) Pain relief occurred in many other types of cancer so treated.(614) One reason for this is that bacterial vaccines stimulate the production of endorphins.

Vitamin C: Large doses of ascorbic acid or sodium ascorbate given intravenously or orally can markedly ameliorate cancer pain.(120) It is of interest that long ago citric acid was used as a dressing or poultice on ulcerated inoperable breast cancers with "instantaneous relief of pain lasting six or seven hours," when fresh applications were sufficient to again control the pain.(141)

Acupuncture is a method of pain control first developed in China many centuries ago. It involves the insertion of needles into certain critical areas of the nervous system, thereby deadening and controlling sensation. It is being now used for alleviation of cancer pain by some oncologists in Western countries.

Psychological Management: Oncolgists rarely recognize the importance of taking the patient's psychological needs into consideration in formulating a treatment plan. Anxiety and fear can lower the threshold of pain while reassurance and support often dramatically raise the threshold and prove as effective as analgesic drugs. When a breast cancer patient sees her lesions growing or her pain increasing despite treatment, she may feel abandoned. The psychological support of a patient is therefore critical and can in fact facilitate ongoing oncologic treatment.(38)

Psychological management of pain includes not only support but utilization as needed of individual or group therapy, and of specific techniques such as hypnosis, meditation and relaxation. As discussed in the chapter on Psychological Adjustment we indicate that it is vital for a patient to take an active part in her therapy. This decreases her sense of helplessness and the anxieties associated with pain, disease and death. (see page 195.)

Hypnosis: The technique of hypnosis is being used increasingly in the management of cancer pain. Hypnosis can be learned and skillfully employed by the physician, the consulting psychologist or psychiatrist and the nursing staff.(38) It should be noted that not every patient is a good subject for hypnosis. Pain control can range from moderate to total analgesia.

Hypnosis has no unpleasant or destructive side effects. It does not reduce normal functioning and does not mentally incapacitate the patients in any way, nor do they develop tolerance to its effects. It can be used to promote life-enhancing attitudes in patients and their attitude toward their cancer can be altered in beneficial ways.

Conclusion: Intractable pain associated with cancer of the breast is rare and can be managed in a variety of ways, depending on its cause, the prognosis and the patient's wishes. In all cases, however, treatment should be tailored to the individual patient.(875a)

PSYCHOLOGICAL REACTIONS OF THE PATIENT, HER FAMILY AND THE MEDICAL TEAM TO BREAST CANCER*

Introduction

The traditional clincial care of the breast cancer patient, oriented as it is to the physical attributes of the disease, has often neglected the emotional effects of the disease on the patient and her family. Breast cancer patients are afraid of the diagnosis of the disease, its treatment and the possibility of recurrence or metastases.(24a) Such fear and anxiety can be immunosuppressive.(5) By alleviating these feelings the patient's response to treatment may be improved.

In this chapter we outline the psychological effects of breast cancer and suggest how those treating the patient can understand these effects and best help her and her family.

Fear of Breast Cancer and its Treatment

Breast cancer is the most commonly occurring cancer in women. Not only is the mortality rate high, but the most widely used surgical procedures, (radical and modified radical mastectomies) are severely disfiguring operations. The loss of a breast and the surgical disfigurement are devastating to a woman's self image and to her sense of femininity, to her sexuality and sexual desirability. Chemotherapy may cause loss of hair and thus further injure this self image. In addition, recovery from surgery, radiation and chemotherapy is frequently slow, painful and debilitating. The patient's shock and trauma at learning of a malignancy that requires breast surgery often produces intense emotional reactions. Such behavior is to be expected. These reactions are more salutary than those of becoming more numb and withdrawn, or of feeling it is undignified to show any emotion.

Even if initial treatment is successful, the patient faces the possible development of cancer in the other breast, of metastases elsewhere in the body, and ultimately of possible death from the disease. The young patient may have a strong reaction as the operation suddenly forces her to confront her own mortality.(13) The patient's fear is also increased by the sudden change in the attitudes of those around her. Family, friends and members of the medical team often find it hard to communicate openly and warmly with the patient. They start withdrawing and in some cases they may even avoid the patient.(29) They try to shield the patient from medical information, as well as from their own fears and feelings. They minimize the severity of the illness, or treat the patient as if they were paying their last respects. These attitudes add to the patient's sense of isolation, making her feel that the gravity of her situation is being unappreciated. She may feel that she herself is overreacting, or that her case is hopeless.

In turn the patient's isolation makes it hard for the medical team and family to reach her with either information or support. This malaise can be transmitted to her family by the patient herself through her own distorted selfview as a person unable to readapt to

*Note: The references to this chapter are given immediately after it. The references to the rest of Part I are then given separately.

her normal role. Children can develop school problems as a response to their mother's depression. Many husbands who are full of uncertainty and conflicting emotions express their concerns by withdrawing and the wives then interpret this as rejection.(10a,28) The husband should be impressed with the importance of his role in his wife's post-operative adjustment and the future of the marriage in general. His reaction to the incision or scar will contain elements of shock, disappointment and anxiety. These are the same feelings that his wife is experiencing and it is important that they share them together. They should be encouraged to seek psychological counselling if needed.

Any mastectomy patient who suffers the loss of a breast needs to mourn the loss of this part of herself. The degree of sense of loss will vary according to the degree in which her sense of femininity and self is invested in this part of her body. The medical team, her family and friends must recognize the patient's need to mourn her loss. By giving her the support to go through the mourning process, recuperation will be considerably enhanced.

It is not surprising that breast cancer patients suffer depression, problems in their family life, disruption of sexual intimacy and difficulties if and when they return to work. The reactions are often more severe with the diagnosis of metastatic breast cancer.(55) It is important to note that the psychological well being of patients who have had the less radical operation is far superior to those who have had radical mastectomy.

Patient's Attitude Toward Treatment and Medical Personnel

The patient is profoundly affected by the attitudes of every single person with whom she comes in contact in the course of diagnosis and treatment of breast cancer. It is therefore vital for all medical personnel to be aware of the relationship between the medical and psychological aspects of the disease. This consideration will make diagnosis, primary treatment and aftercare more tolerable for the patient.

In the course of treatment the breast cancer patient comes into contact with a great many different specialists, technicians, nurses, social workers and secretaries and also with those involved with aftercare and rehabilitation. She may be admitted into one or more hospitals as an inpatient, as well as having later therapy as an outpatient. The resulting confusion, trauma and distress only add to the burden the patient must bear.

Efforts have been made by using the team approach to counteract these problems. However, unless unified case management is provided and there is concern for the patient herself, as well as for her illness, such techniques may be efficient but impersonal. Non-involvement is made so much easier by the "team approach," which can so insidiously become 'screen withdrawal,' where the doctor, perhaps unconsciously, uses the team as a screen to protect him from involvement with individual patients. This is not an attack on the team approach, which has certainly brought many benefits, but which, wrongly used, is capable of great harm, and of eventually causing neglect of the patient.(15)

The continuing support of the office or clinic staff is also vital to the patient during further treatment. Such support represents the one constant factor in the confusing and changing process of the various therapies which may be required.

Relationship between Patient and Physician

We recognize that the development of a good relationship is the responsibility of both the patient and the physicians who treat her. However, not enough physicians are aware

of the crucial nature of this relationship for breast cancer patients, or have the tools to develop trust. These include the skills of communication, sensitivity to the unique qualities of each patient's character and background and the willingness to allow her the dignity and responsibility of helping to make decisions. Above all it is the *quality of time* the physician spends with the patient.

The ability of the physician to listen, his openness with both the patient and her family, and his treatment of the patient as a responsible person, will lead to mutual respect and confidence. This confidence, based initially on the medical expertise of the physician, will thus include those factors which will strengthen the patient's ability to cope with the disease and its treatment. Sensitive listening is especially important when the team approach has been emphasized as Ellis noted, "The odds are, though, that the patient's responsible medical attendant spends a good deal more time in his office, writing about the patient, or talking to group meetings about the patient, or at seminars about similar patients, then he does *listening to the patient*. This 'non-caring care' is not good enough, and gives the profession a bad name. No matter how clever or how highly qualified a physician is, if he does not care to, or cannot relate to, his patient as a person, he cannot, in fact, be really concerned with 'the psychological process in the patient.'(15) This is particularly problematic when the physician is an oncologist.

Trust, the most important ingredient in this relationship is not instantly won but must be carefully built. The patient initially comes to the physician to benefit from his medical knowledge and experience. Her utilization of his expertise will be severely limited unless she trusts him as a person as well as a physician.

There are many components to the establishment of trust; the first of which is that the patient must at all times be seen "as a person" not just the bearer of a disease. This demands time, care and courtesy all of which are often hard for an overworked physician to give his patient. Trust is created by being open with the patient and by being emotionally supportive.

Physician's Attitude Toward the Patient and Treatment

To our knowledge there is no literature as to the effect on the surgeons of having to cope with hundreds of frightened and anxious women on whom they are to perform a much dreaded and mutilating operation. We expect the surgeon, not only to be a superbly trained specialist, but we ask him to be caring and concerned for each one of his patients. The patient should recognize that it is not easy to be a skilled and caring breast cancer surgeon. The detachment of the surgeon may be experienced by the patient as callousness. We suggest that the surgeon is defending against his own feelings and is not always able to consider the feelings of the patient. Levine has done pioneer work in trying to get oncologists to be aware of their own feelings as well as those of the patient. He is concerned about defenses that are crippling physicians dealing with their cancer patients. He helped to developed a series of seminars at the National Cancer Institute for oncology fellows to help them verbalize their deep-seated problems in treating cancer.(3) We believe that oncologists dealing with breast cancer have a particular need for such ongoing training.

A cancer patient who is also a physician has stated that living with cancer is similar to the isolation of solitary confinement. "The most useful people and the best doctors, are those prepared to come inside the cell, sit down and spend some time with you."(35) Unfortunately, many oncologists merely remain outside and note the objective facts by peering in the door. They are unprepared or unwilling to share the patient's space.

Communication of Information

Much of medical education is devoted to learning how to gather and evaluate facts; little is devoted to how to communicate them. Souhami points out that most medical students have no chance to discuss with their teachers the difficulties of talking to cancer patients. He describes how he has helped solve this problem at University Hospital in London.(57) Not only is the initial training in medical school limited, but physicians seldom recognize the need for ongoing studies. It is now recognized that how a message is given is as important as what is said. The mode of communication determines what information is received by the patient, how much is received, absorbed or blocked. In the art of communication the responsibility of conveying a message rests with the sender. Lack of accurate reception or distorted perception can be deleterious to the treatment process.

Every spoken message contains verbal and non-verbal elements. The non-verbal elements include the speaker's facial expression, eye contact, body posture, touch and tone of voice. Often what is said is not supported by these non-verbal messages. It must be remembered that in such instances the non-verbal cues are always the stronger. (i.e., It is not what you say, but how you say it.) Words convey facts and ideas, nonverbal cues indicate feeling. Communication reflects attitudes as well as information. Non-verbal contacts between medical staff and the patient and her family are critical indicators of the quality of the relationship. Good communication helps to counteract the intimidating atmosphere of most hospitals and the indignities that so often accompany serious illness. In such an impersonal setting even greater attention must be paid to the human needs of the patient.

It is necessary to impart accurate information to the patient about her diagnosis, treatment and prognosis. The patient who is uninformed remains as an outsider in her own treatment, a child who is not strong enough to receive information, or wise enough to take part in decisions. All too often medical terminology, incomprehensible and confusing to the patient, is used, and the physician may not realize the communication gap. This demands great sensitivity on the part of the physician as to timing, how much information she is able to tolerate and the accuracy of her reception of information. This kind of sensitivity is reflected in Howell's statement: "No one had taught me during my professional training how to translate medical terminology into words, phrases and ideas that could easily be understood by my patients. The patients taught me."(20)

The aim should be one of total openness. The patient will tend to deny, to block out what she cannot tolerate, but on the other hand, she may be acutely sensitive to attempts by her physician or family to withhold information or present misleading or false information. The physician must frequently check to determine if the patient has absorbed the information and if it is correctly perceived.

Initial Interview

During the initial evaluation there are many crucial factors which must be considered and are too often neglected. The patient's ability to cope with her disease is affected by psychological and social factors including both exogenous and endogenous stress. It is important for a physician to take into consideration the cultural and social background of each patient. For example, some cultures tend to repress their feelings and this can affect the response to treatment because such behavior is immunosuppressive. He will thus be able to understand and monitor her coping mechanisms more efficiently. The

initial interview for breast cancer patients is extremely important and sets the tone for physician and patient. If at this time the physician appears hurried or distracted, great harm can be done. In every contact it is the quality of time which is obviously crucial.

In the section on endogenous factors affecting incidence of breast cancer it was stated that in many cases the onset of the disease was preceded by severe psychological stress, e.g., loss of a major relationship through death or separation. These patients tend to repress their feelings. It is interesting to note that after bereavement there is a depressed lymphocyte function.(5)

It is vital to identify patients who have suffered such stress, because of their possible need for psychological counselling, and also because they may unintentionally mislead their physicians by denial of both physical and psychological symptoms.

There are in addition those patients with acute family, financial and/or professional responsibilities, for whom the disease creates special problems.(17a, 34a) Such concerns make it impossible for them to focus adequately on their illness and treatment. Again it is essential for the medical team to recognize such patients and to alleviate their anxiety by identifying and obtaining the social services or community resources which are necessary.

Many breast specialists are unaware of the resources that are available. For example, the Reach to Recovery Program, and the availability of home care services provided by the American Cancer Society, mutual support groups, as well as agencies like the visiting nurse services and the Social Service Departments of most large hospitals are also helpful. If no mutual support groups are available, physicians should encourage their breast cancer patients to start one.

As stated above, it is vital for the physician to maintain close and open contact with the patient's family or other concerned persons, and to encourage the patient to share her information and feelings with her family.(10a) The physician's ability to help his patient to utilize her family support system can be vital, not only during primary treatment, but also in the rehabilitation process. The idiosyncracies of each patient's physical and psychological components and the increase in variety of treatment alternatives emphasize above all the physician's need for flexibility.

SPECIAL NURSING CONSIDERATIONS

It would be an important contribution to the management of breast cancer patients if a better communication could be established between the surgeons and the nursing staff of surgical wards. It is clearly going to be important to decide who tells the patient what and when. This used to be the role of the doctor, and if he did not do it or did it badly, nevertheless he alone had the responsibility for it. But in recent years the nursing profession has developed its own level of expertise in interpersonal relationships. However, it should be the responsibility of the surgeon *and* the nursing staff to have a clear communication so that it can be determined who is going to communicate with the patient and so that no conflicting views about her condition will be given.(21)

What the nurse discusses with the patient during the preoperative period should be individualized to her needs and level of understanding. A member of the nursing profession describes them as follows:

1. A description of the diagnostic procedures to be used and an explanation of their purposes and side effects.

2. Make sure the patient and her family understand that if excisional biopsy results are positive, a mastectomy may be recommended. The patient should realize that there are simple, modified radical, radical and supra-radical mastectomies as well as more conservative procedures, such as lumpectomy or wedge resection which may be feasible if the lesion is very small and of a less malignant type. She should also be told that modern radiation therapy may be possible in lieu of surgery or as an adjuvant to lumpectomy if the patient refuses mastectomy. She can choose to postpone further surgical procedures until she knows the results of the biopsy. These points relating to surgery should be discussed with the surgeon, but sometimes he does not outline all the possible alternatives.
3. Descriptions of the immediate post-operative side effects following radical or modified radical mastectomy, such as tightness of the arm, phantom breast syndrome and difficulty and pain in coughing. (Others are described on pp. 44–48). Explain some of the nursing procedures that will be used to deal with these problems such as a raised bed to promote drainage, arm exercises and coughing exercises.
4. Let the patient and her family ask questions and share concerns about the operation and postoperative period.
5. Nursing care for the post-op mastectomy patient will vary according to the extent of surgery, and the patient's general attitude and acceptance of the procedure. This can be a stressful time for the patient, physically and emotionally, and the nurse can provide a great deal of support at the bedside.
6. To reduce the patient's anxiety about pain, reassure her that she can have pain medication every three to four hours or as ordered. She can be made more comfortable by supporting her arm on the involved side with a pillow, unless the surgeon orders otherwise; she can be helped with coughing and deep breathing exercises every two hours and within 24 hours she can be assisted in getting out of bed and walking briefly unless there are medical orders to the contrary. She should be encouraged to wash her face, brush her teeth and comb her hair. (Arm exercises are described below on p. 00).

After a mastectomy a woman may undergo chemotherapy. The nurse's involvement continues to be important because the woman may be apprehensive about the side effects and long term results. When radiation is used, the nurse may also help to reduce the patient's anxiety by giving her the basic information she seeks. Nurses may benefit by reading Peck and Boland's excellent papers on emotional reactions to having cancer and to having radiation treatment.(44;45)

Nurses beginning to work with breast cancer patients should also be aware of the common side effects to radiation and chemotherapy.

Side Effects:	Nursing Implications:
1. nausea and vomiting	—control with antiemetics as far as possible. —light meals and fluids recommended prior to therapy. —supplemental feedings may be necessary.
2. diarrhea/constipation	—check bowel function early so appropriate measures may be taken.
3. stomatitis (inflammation of the oral mucosa)	—mouthwash of half strength, peroxide and water QID prophylactically and continued for a week. —lubricant (Vitamin A-D-E ointment to lips to avoid drying and cracking). —mycostatin mouthwash if candida infections occur.

Side Effects:	Nursing Implications:
4. alopecia (loss of hair)	—if physician in charge permits, ice packs to the scalp during and after each treatment for two or three hours can prevent this. (Special head packs are available commercially.) —if not, reassure patient that her hair will rapidly grow back when drugs are stopped. —advise patient to have a wig ready for use if needed. These are provided free in New York City by the American Cancer Society for patients in need financially.
5. bone marrow depression (usually occurs 10–14 days after chemotherapy)	
a. thrombocytopenia	—observe patient for bruising, petechiae and purpura —note nose bleeds, hematuria or heme-positive stools *If platelet count decreases drastically* —place signs at patient's bedside indicating the following: —do not give IM or SC injections —apply pressure after blood is drawn —do not give aspirin, it may act as an anticoagulant —keep patient's temperature normal (high temperatures shorten platelet life) —avoid any trauma
b. leukopenia (low white blood cells)	—avoid exposure to infections from staff, visitors or environment —insure meticulous personal hygiene; infections are often due to patient's own bacterial flora
c. anemia	—assess energy demands placed on patient and reduce if necessary

Post-Mastectomy Exercises

The role and timing of physical therapy following mastectomy has not received much study. However, a prospective randomized clinical trial was carried out at the National Cancer Institute which revealed that patients randomized to receive early arm motion had more total wound drainage, more days of drainage and later post-operative discharge than did patients who started motion on day seven. Wound complications including infection and small areas of skin breakdown occurred more frequently in the early group. There was no difference between the two groups as regards achieving functional full range of motion. The early institution of flexion and abduction exercises following radical mastectomy and axillary dissection thus appears to have a deleterious effect on wound healing and drainage.(32)

Unfortunately many surgeons, except in the larger cancer centers may pay too little attention to this aspect of rehabilitation. Nurses should become familiar with the suggested arm exercises and encourage patients to do them, but warn them against beginning them too soon.

Wall Climbing—stand facing the wall with feet apart and toes as close to the wall as possible. Palms should be placed on the wall at shoulder level with elbows bent. Flexing the fingers, "walk" the fingers of both hands up the wall parallel to each other until both arms are fully extended. Then work the hands back down to shoulder level.

Arm Swinging—bend forward from the waist with arms hanging toward the floor. Swing both arms from side to side, front to back and in a circular motion in both directions.

Rope Turning—tie a 6 foot rope onto a door knob. Stand a few feet away from the door and grasp the free end of the rope in the hand of your affected arm (other hand may

be placed on hip). Keeping the wrist and elbow straight, turn the rope in circles. Begin with small circles and gradually increase to larger circles.

Pulley—toss a rope over a shower rod. Hold one end of the rope in each hand. With both arms extended away from the body, pull left arm up by tugging right arm down then pull right arm up by tugging left arm down, using a see-saw motion.

Touching Forehead—stand facing the wall with arms extended and palms flat against the wall. Lean body forward towards the wall until forehead touches the wall. Push away from the wall back to original standing position.

Psychological Support

In the past nursing service was organized in such a way as to protect the individual nurse from emotional stress and anxiety arising from her involvement with the problems of individual patients. This led to restricted contact with any one patient. Radical reforms in nursing education are breaking down traditional barriers to communication with patients and an awareness of previous neglect of emotional and psychological aspects of care has become apparent.(11)

During the initial admission interview with the patient, the nurse should begin her assessment of the woman's fears and anxieties, her coping behavior and her intellectual and emotional capacity for understanding what is happening. The nurse should also be aware of the way the patient interacts with her family and close friends; these are the individuals who can be mobilized later to provide support and understanding.

The majority of patients with breast diseases are admitted for an excisional biopsy and possible mastectomy. The nurse must quickly find out what the patient has been told by her physician about the disease, whether she realizes a mastectomy is possible and how much she knows about the procedures involved. Experience has shown that it is valuable for both patients and staff to encourage free and open communication between the patient and those caring for her.

There is abundant evidence that the majority of breast cancer patients prefer to talk about their disease, rather than the old idea that "none of my patients want to know." Helping the patient to adjust is a dynamic process and cannot be done effectively in a single conversation. The good communicator places himself alongside the patient as friend and ally. Nurses are unique among health care professionals in that they spend their whole working day within the reach of their patients—an ideal position to act as communicators and counsellors. By listening with sensitivity, nurses will be able to understand what the impact of breast cancer means to the patient's personal and professional life, and will be able to use her particular professional skills to offer advice and support.

Because the breast cancer nurse is a woman, her patients often find it much easier to express their fears and anxieties to the nurse than to a male doctor. The nurse can facilitate communication by talking with the family and patient separately and together and can assess their reactions and ability to adjust. She should encourage them to express their feelings to each other. She should try to encourage the participation of family members who seem reluctant to get involved; if there are children, assess the degree to which they are being allowed to participate in the family crisis and encourage their participation at a level appropriate to their age and maturity. Family members who have difficulty communicating with each other directly may often turn to the nurse as an intermediary—a difficult, but important role, which often helps to break down barriers between the patient and her family. The end result may greatly relieve stress and tension which can be immunosuppressive to the patient.

After mastectomy, women are physically recovering well, but the emotional wounds are still raw. They find it hard to look at themselves. Their self-image is low; their relations with their husbands, children, family and friends may suffer. The nurse should be observing the patient for signs of depression, withdrawal, insomnia, lack of appetite and acute anxiety. She should try to get her to talk about her feelings and if necessary help her seek further support services and specialized counselling for herself and/or her family. Some hospitals or cancer centers have breast rehabilitation programs that begin in the hospital.

Rehabilitation

No program concerned with the management of the breast cancer patient is complete without including effective rehabilitation. This includes consideration of the physical, functional, vocational and sociopsychological needs of these patients. Rehabilitation planning should begin with the diagnosis. It is not only the person who has been cured of cancer who is entitled to rehabilitation; the person whose anticipated survival may be less than average should not be deprived of the right to continue as a social and economic entity with a productive existence, for as long as her physical state permits.

Rehabilitation of the radical mastectomy patient has three main goals: maintenance of arm and shoulder range of motion and function, restoration of cosmetic appearance and psychological adjustment.(12)

Arm care rules, active exercises and positioning are taught the patient in an effort to prevent lymphedema and restriction in range of motion. If lymphedema does develop, it may respond to a combination of medical and local measures, or occasionally to surgery.

Cosmetic appearance may be restored through reconstructive surgery. The possibility of such a procedure should be discussed by the surgeon with all patients who are possible candidates. This should preferably be done prior to surgery.

Several volunteer programs in this country and in England offer good support services, i.e., The Reach to Recovery Program. Women who have had the operation and who understand the emotional and practical aspects of adjusting to it are thus available to talk to patients; discussing emotional implications, activities, exercise and sources and styles of brassieres. This was started 30 years ago by a mastectomee who ran it as a private foundation for many years. It is now administered by the American Cancer Society. Reach to Recovery volunteers only visit the patient if the surgeon has requested it. Unfortunately, many surgeons remain unaware of this program and therefore many patients are deprived of it. At present these volunteers only reach about half the mastectomy patients.

Prosthesis

Choosing and being fitted for the correct prosthesis has been a process unnecessarily filled with trauma, confusion and disappointment. Much of this could be minimized if the patient were given some preliminary information during her hospital stay. If the physician, nurse, social worker or Reach to Recovery volunteer can suggest a list of recommended shops or fitters this will be a comfort. It is wise for the nurse to have some literature on hand and to explain to the patient what options are available.(65)

The sensitive and skilled fitting of a well accepted prosthesis is possible and can mean the difference between prompt, cheerful and total mobilization and long term personal distress. The asymmetry of a single remaining breast can cause shoulder, neck and back

pain. Postural changes are common, with the affected shoulder rising. Apart from the orthopedic aspects of the situation, the emotional comfort of a correct silhouette is immense.(11)

It is not easy to go and buy the first prosthesis. The patient must disrobe and come face to face with the deformity, realizing its scope and permanence. A kind and patient fitter is invaluable. Deanseley encourages patients not to go alone, but with a sister, mother, husband or friend.(11) The prosthesis that, with its brassiere, gives the most comfortable and acceptable silhouette is best. They are not cheap, but most health insurance programs cover the costs provided annotated receipts are presented. Nurses should apprise patients of this fact.

Prostheses range in price from $5.00 for a foam-rubber filled to $500.00 for custom-made sculptured models. The most popular form is the silicone filled type at $125.00 to $160.00.

The surgeon should be consulted before the patient selects a prosthesis especially in regard to its weight and to the width of the brassiere strap. A large breasted woman, for example, may need a more heavily weighted prosthesis for comfort and balance. If extensive surgery was performed a wide strap brassiere is in order as a thin strap could possibly create a tourniquet-like effect in the shoulder area.

For the small breasted woman who has had less extensive surgery (a simple or modified radical), a less sophisticated device will often do. Some women find that a "dime store falsie" is suitable to their needs. However, the unweighted foam forms tend to ride up, so that even smaller women may prefer the silicone type that more closely matches their natural breast.

Some women wish to wear their preoperative brassiere when they leave the hospital and this can be done using soft cotton or simple clean padding to fill the side that has been operated. The literature from Reach to Recovery gives sewing tips on converting existing brassieres to accommodate a prosthesis.

Patients need not rush to obtain a permanent full prosthesis, since it should not be worn until about six weeks after surgery. Once a prosthesis is purchased it can be worn day and night. Some patients will benefit from a breaking-in period, gradually wearing it for a longer time each day. Wearing it in bed at night may help prevent stiff neck and shoulder problems in some cases.(11)

Choosing the Clothing to Wear After Mastectomy*

Appearance and clothing are a major concern of the post mastectomy patient and one that she feels uneasy discussing with male physicians. To help a patient visualize what her scar will look like when it is healed, the nurse or the physician can make a drawing. This approach is especially helpful in preparing the patient to look at her incision. The nurse can then go on to discuss clothing and prostheses more realistically.(65)

Once she is fully healed the postmastectomy woman will be able to wear most of the clothes she wore before surgery. However, special mastectomy boutiques are springing up throughout the United States and they will send catalogues on request. If the nurse has this material to discuss with the patient it will go a long way in establishing rapport.

In Hospital: Opaque nightgowns are best. The patient should choose one with a wide drawstring neck which can be dropped from the shoulders when the doctor or nurse needs

*This section is taken from W. A. Winkler's excellent report.(65)

access to the operative area. If a robe is needed it should have a deep armhole. A temporary brassiere and breast form can be worn while the patient is still bandaged, especially when receiving visitors. These are furnished by the hospital or by a Reach to Recovery volunteer.

Immediate Post-Hospital: The patient will be heavily bandaged when she leaves the hospital. One immediate essential is a loose, button front deep armhole shirt or blouse. They are available in most active sportswear shops or department stores. Some mastectomy boutiques have designed their own. At first the patient should be encouraged to wear loose fitting garments if she is at all apprehensive. Back zippers on dresses can be a problem until full arm motion is regained, therefore zipper pulls available at notion counters are helpful in this period.

Long-Range: The only possible limitations besides low-cut nightgowns are bathing suits and evening gowns. Even with these, some women have few limitations depending on how extensive the surgery has been. Special nightgowns have been designed by both the prostheses manufacturers and the mastectomy boutiques. Some are designed to accommodate a prosthesis, some are available with a special "sleep puff," and some are designed to be worn with no prosthesis with fullness at the neckline so lack of symmetry is minimized. The radical mastectomy patient should avoid garments with tight sleeves and armholes because her arm might swell. As noted elsewhere tight bracelets and watchbands on the operative arm should be avoided, also heavy handbags or packages should not be carried on that arm. (See above p. 47 for details on the prevention of lymphedema.)

(Further information on where to obtain prostheses and clothes in the United States can be found in reference #66.)

Discharge Planning

Social workers and medical teams should consider the following elements with the patient:

1. *Type of out-patient treatment* and follow-up visits to the physician or clinic. If patient is elderly or infirm, arrangements for transportation must be arranged.
2. There are those patients who need *nursing and/or homemaker care* and they may not have the funds or the knowledge to arrange it. Special attention must be paid to such patients and provision made for home care.
3. *Nutrition.* The patient should be advised as to her nutritional needs. Too few oncologists are aware of this. (See above p. 112.)
4. *Finances.* Medical and social work team members should be particularly aware of any financial concerns that a patient may have, insurance coverage, etc. Acute anxiety over such matters are detrimental to her recovery.

   The American Cancer Society provides certain resources such as transportation and short term homemaker care. They also provide free wigs for needy patients who have lost their hair due to chemotherapy.
5. *Occupation.* Almost all breast cancer patients can return to their former job without limitations. However, others, whose occupations involve strenuous use of the affected arm should seek the advice of their oncologist. Patients receiving radiation or chemotherapy must limit their activities during the treatment period.
6. *Family.* As mentioned above, there are those breast cancer patients who have the added stress of difficult family situations. There are also those who have no family

or close friends. This lack of support is an added stress for both groups of patients. Attention must be paid to their particular needs in order that they may fully benefit from treatment.

7. *Psychotherapy*, either individual or group, can be extremely effective at this time of crisis in helping the patient to adjust. As stated above, marital counselling may often be needed to resolve sexual and emotional problems. These problems may be alleviated if the surgeon has discussed the possibility of breast reconstruction.
8. *Social Support in the Illness Experience*. The stigma associated with cancer often leads to avoidance behavior and withdrawal of support by friends or family. Peters-Golden studied this problem in 100 breast cancer patients and 100 healthy individuals.(44a) Patients reported non-materialization of expected support networks and decreased adjustment due to this experience. They also asserted that the support extended to them is often inappropriate in nature, due to the assumption that the most salient concern of a mastectomized woman is the loss of her breast, rather than the fact that she has cancer.
9. *Mutual Support Groups*. These groups have proved to be extremely effective in helping breast cancer patients to adjust to their situation. Many oncologists do not refer their patients to such groups because they are unaware of their existence or their value. The patient should be encouraged and helped to start such a group if none exists in her community.
10. Use of *Meditation and Relaxation Techniques* as reported by Meares in Australia and the Simontons in this country have proved helpful and should be considered by breast cancer patients.(1;56–58)

In conclusion, we would like to advocate some degree of special training for individuals who are involved in the handling of breast cancer patients both in and out of hospitals.

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PART II

The Immunopotentiating Effects of Concurrent Infections, Inflammation or Fever

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Introduction

As noted above on page 36, for over 200 years physicians have observed dramatic "spontaneous" regressions of various types of neoplastic disease during or following acute concurrent infections.(602–619)* A large number of authors recorded their observations of the beneficial effects of such infections, as well as those in which inflammation, fever or incomplete surgery were involved. Our infection monograph contains 1,032 references. We have also assembled many more such cases that were seen all over Europe and the United States but had not been published.

Vautier (1813) discussed the question of whether cancer may be cured by the sole forces of nature. He had found "several cases in searching the writing of the most careful observers in which cancer terminated happily by the development of gangrene." (858) We have abstracted 22 such cases in which "gangrene" developed spontaneously or by inoculation, of which the majority were breast cancers.(611) Recent research on the Tumor Necrosis Factor suggests that in these patients a combination of bacteria had induced the tumor necrosis factor which these early physicians had designated as gangrene.(611)

Such cases inspired physicians in the 18th and 19th century to induce "laudable pus, setons or issues" in their inoperable cancer patients as the first form of immunotherapy.(816)

It is clearly evident that concurrent viral infections may *lower* the resistance of cancer patients and may play a role in the development of the primary, the more rapid progress of the disease or its reactivation.(611;617)

The data assembled here clearly indicate the powerful therapeutic effects which various types of bacterial infections may exert in breast cancer. However, modern oncologists tend to see only the life-threatening bacterial infections which develop in terminal cancer or leukemia patients following immuno-suppressive conventional modalities; hence they are not clearly aware of the beneficial effects such infections may have if they develop prior to the terminal stage or before such therapy is given. The indiscriminate use of antibiotics should be avoided in cancer patients, instead one should administer injections of mixed bacterial vaccines to stimulate and reinforce the immune defenses. This procedure is being used in certain burn units to prevent infections in these severely compromised patients, and in treating cancer and leukemia at the present time.

*References refer to bibliography for Part I

Part II, SERIES A:
INOPERABLE MAMMARY CANCER WITH CONCURRENT PYOGENIC INFECTIONS, INFLAMMATION OR FEVER: 33 CASES CARCINOMA, 2 CASES SARCOMA

Physician, Date References	Sex Age	Diagnosis Extent Disease	Treatment Prior to Infection	Subsequent Treatment	Type of Infection	Immediate and Final Results
1. Quesnay 1749 (68; 82)	F adult	enormous ulcerated carcinoma	none	none	suppuration; entire tumor gangrenous; septicemia	*growth became quite soft, almost painless*; death from pyemia
2. Lambergen 1757 (47; 68)	F 34	scirrhus carcinoma lt. breast	belladonna infusions (orally)	belladonna infusions for 17 mos.	prolonged suppuration, sinuses discharged	*complete recovery*; *remarried, had a child, breastfed it*; end result unknown
3. Marteau 1760 (55; 68; 98)	F 49	extensive scirrhus carcinoma rt. breast	cathartics, laudanum, belladonna	conium pills, 12 grains daily for 3 mos.	erysipelas with pus	*almost complete disappearance*, bean-size nodule remained; end result unknown
4. Dupré de Lisle* 1774 (19; 68; 98, case 80)	F adult	inoperable carcinoma	"all the most effective remedies including conium pills without effect; condition hopeless"	new wound opened at site of former abscess causing further suppuration	abscess on leg, with suppuration: "against advice patient allowed it to heal"	*"as abscess increased suppuration became more abundant, breast cancer diminished until no trace remained"*; it immediately recurred when abscess healed; when suppuration again well established, *recurrent growth again gradually regressed*; end result unknown
5. Martinet 1781 (56; 68)	F 66	enormous, very advanced firmly fixed carcinoma lt. breast, metastases extending from axilla to sternum, clavicle to costal margin; hemorrhages from eroded blood	weak ammonia compresses applied locally	compresses 3 times a day for months	local infection; tumor mass broke down, abundant suppuration lasting several mos., (no fever)	*mass decreased 50% in few hrs., next day no longer adherent*; *pains ceased*; *gradually regained strength*; *steady improvement for 4½ mos., 5 sin-*

		vessels; 14 ulcerated areas, suffocating odor; cachexia, condition desperate				*uses healed*; as suppuration diminished, pains returned, nodules increased in size; *further regression, leaving white healthy scars at site of former huge growth*; end result unknown
6. Garneri 1810 (2; 37; 68; 98, case 51)	F 50	inoperable carcinoma involving entire lt. breast in one confluent mass, pain became unbearable; of 18 mos. duration	untreated	none	"putrid low grade fever" for 12 wks.: pain free during fever; inflammation and gangrene then developed in affected breast	pain reappeared on 15th day of fever, worse than before; *whole tumor mass entirely destroyed by inflammation and gangrene, ulcer completely healed by 56th day; returned home an apparent cure*; end result unknown
7. Vautier 1813 (68; 104)	F 50	inoperable scirrhus carcinoma lt. breast of 2 yrs. duration, very severe pain; sanious very fetid discharge	incised 18 mos. after onset, no pus found; Dupuytren enlarged wound to facilitate drainage	none	laudable suppuration then developed	*complete regression*; end result unknown
8. Vautier 1813 (68; 98, case 37; 104)	F 46	inoperable nodular carcinoma lt. breast size of turkey egg, overlying skin bluish due to enlarged veins; acute pain especially on sudden movements	conium pills; poultices of scraped carrots and conium leaves; "cautery" opened on side of tumor	conium pills gradually increasing doses; 2 leeches	very severe erysipelas in tumor area; suppuration for 7–8 days	tumor diminished considerably in size following medication and "cautery," pain decreased; *during erysipelas tumor softened and decreased markedly*; "pain recurred a few mos. after the cure," disappeared after application of leeches, regained former robust health; end result unknown
9. Richerand 1815 (48; 68; 84; 98; 104)	F 48	inoperable very hard carcinoma rt. breast; lancinating pains	untreated	untreated	violent inflammation attacked the skin of the breast and all surrounding tissues, tumor softened, gangrene developed	*whole tumor mass detached itself from chest wall with the enormous eschar leaving healthy looking ulcer which healed in 2 mos.*; end result unknown

PART II, SERIES A: INOPERABLE MAMMARY CANCER WITH CONCURRENT PYOGENIC INFECTIONS, INFLAMMATION OR FEVER, (cont'd)

Physician, Date References	Sex Age	Diagnosis Extent Disease	Treatment Prior to Infection	Subsequent Treatment	Type of Infection	Immediate and Final Results
10. Dupuytren 1831 (20; 68; 98, case 54)	F 40	extensive terminal scirrhus carcinoma of breast of 18 mos. duration, bedridden, cachetic, almost moribund	surgery refused	compresses of chlorinated water; necrotic tissue evacuated or cut off	"for several days breast felt as if air was circulating in it"; inflammation, fever, emesis for 48 hrs., gas gangrene in deeper portions; 3 incisions; evacuated large quantity viscous fluid; large part of breast became necrotic	*growth regressed 30% in 8 days; complete regression in 4 wks.; considered cured*; end result unknown
11. Fristo 1831 (36, p. 40; 68; 98, case 53)	F adult	enormous ulcerated breast carcinoma involving axillary lymph nodes, unbearable pains and odor	dilute calcium chlorate caused improvement	none	gangrene	*skin and breast tissue became necrotic; ulcer became healthier; finally healed*; solid very extensive cicatrix adherent to underlying tissues, interfered with shoulder movements; *well, NED few mos. later*; end result unknown
12. Boyer 1851 (4; 5; 6, p. 250; 68)	F 46	extensive ulcerated inoperable scirrhus carcinoma rt. breast size of fist, retraction of nipple; bilateral axillary metastases, cachectic; entire arm markedly edematous; dry cough, acute almost continuous pain	leeches, compression; internal resolutives; plasters, iodine, mercurials, conium all tried to no avail	radical mastectomy, axillary dissection very difficult; tissues showed gelatinous degeneration	erysipelas involving anterior chest, part of abdomen; slight fever, postoperative suppuration "of good character," fever for 3 days	ulceration deepened, axillary nodes enlarged, entire arm very swollen, dry cough; *complete healing followed surgery and suppuration; regained lost wt.*; end result unknown

13. Stein 1883 (7; 13; 68)	F 45–48	extensive inoperable irregular, nodular tumor rt. breast, veins dilated; anemia; cachexia	1 injection pyrophosphate of iron with citrate of soda	none	erysipelas 12 hrs. later at site of injection, spread over neck, chest lasting 12 days	*extensive growth regressed during erysipelas* except for 2 small indurated nodules about 3 cm. in diameter; *great improvement in general health*; end result unknown
14. Neelsen 1884 (68; 75)	F 41	bilateral carcinoma, with axillary metastases, size of fist in lt. breast, indurated infiltrating lesion rt. breast	lt. mastectomy, wound allowed to granulate	none	very severe erysipelas with pleurisy, dyspnea 8 mos. post-surgery; 2nd fatal attack erysipelas	*tumor in rt. breast regressed somewhat, overlying skin became gangrenous*; 2nd erysipelas caused death on 10th day; autopsy showed *fatty degeneration, atrophy in tumor*
15. Vulpian 1885 (68; 108)	F adult	recurrent inoperable scirrhus carcinoma lt. breast extensively involving chest wall with metastatic nodules, possible metastases to femur, tibia; of over 2 yrs. duration; terminal	primary removed by Langenbeck 2 yrs. before	iodoform dressings	pyogenic abscess in recurrent growth	*gradual recovery; complete regression of infiltrating recurrence and metastases including exostosis of greater trochanter; NED 4 yrs.* after onset; 2 yrs. after recovery
16. Esteves 1885 (25; 68)	F 70–75	inoperable scirrhus carcinoma rt. breast, several well marked areas of induration, small ulceration	none	none	erysipelas over rt. breast, thorax, shoulder	*nodules first increased 1–2 cm. in diameter; after infection breast became completely flaccid, induration gone;* end result unknown
17. Franceschi 1886 (35; 68)	F 61	recurrent ulcerated inoperable carcinoma rt. breast	mastectomy		erysipelas	*growth regressed; in a short time area entirely healed by healthy granulations;* end result unknown

PART II, SERIES A: INOPERABLE MAMMARY CANCER WITH CONCURRENT PYOGENIC INFECTIONS, INFLAMMATION OR FEVER. (cont'd)

Physician, Date References	Sex Age	Diagnosis Extent Disease	Treatment Prior to Infection	Subsequent Treatment	Type of Infection	Immediate and Final Results
18. Mohr 1888 (61; 68)	F 83	inoperable carcinoma lt. breast, multiple axillary and supraclavicular metastases, also to skin around primary; cachetic, bedridden	surgery refused	none	severe erysipelas from neck to ilium involving diseased area	*complete regression of primary and all metastases, general condition improved markedly, regained former wt., strength;* fell, broke humerus 11 mos. later; *healed rapidly*, no disability; NED 3 yrs. after onset
19. Hutchinson 1892–1893 (13; 42; 68)	F adult	scirrhus cancer or adenoma of breast	untreated	none	very severe, almost fatal erysipelas	*complete regression* during erysipelas, NED 5 yrs. later
20. Perrin 1891 (68; p. 45)	F 64	inoperable carcinoma lt. breast, with axillary metastases (also had an enormous goiter)	breast untreated; goiter operation	none	following goiter surgery breast lesion became inflamed and suppurated	*complete regression leaving a depressed scar;* not traced
21. Eliot 1893 (11; 13; 68)	F adult	recurrent inoperable carcinoma of breast, continued to get worse after surgery	surgery refused for primary until condition far advanced	none	erysipelas developed spontaneously; living cultures inoculated for 2nd recurrence, failed to cause further erysipelas	*some of the recurrent tumors disappeared; general condition greatly improved for 6 wks.*, then again recurred; disease progressed causing death
22. Coley 1893 (11; 13; 68)	F 38	inoperable advanced ''cancer en cuirasse'' ulcerated	not recorded	none	3 severe attacks erysipelas in 3 mos.	*slight breaking down of a few nodules, rapid healing of ulcerated areas but no marked arrest of the disease;* end result unknown

23. Coley & Morris 1894 (13; 68)		recurrent inoperable carcinoma breast	not recorded	none	erysipelas lasting 10 days	*marked decrease in size*; later the growth increased in size; end result unknown
24. Coley & Westbrook 1894 (12; 13; 68)	F 43	ulcerated inoperable twice recurrent scirrhus carcinoma, metastases to both axillae and cervical lymph nodes, far advanced	radical mastectomy 2 yrs. after onset; 2nd operation for prompt recurrence 3rd incomplete operation	none	erysipelas (fever 104°F.) involving breast, axilla to ilium, arm, cervical region; mild attack lasting 5 days, edema of arm	*during 1st 2 days free breaking down and discharge from fungating growth; by 3rd day area "very dry, quite cleaned and painless"*; on 5th day again began to break down rather freely; *arm remained swollen for some days, then subsided "in better spirits than for a long time"*; end result unknown
25. Czerny 1895 (14; 68)	F adult	seven times recurrent carcinoma, markedly infiltrating chest wall	7 operations prior to consulting Czerny; he dissected away as much as possible leaving saucer-size wound with carcinomatous base	none	erysipelas in wound, almost fatal	*recurrent nodules disappeared, complete healing in 8 wks.*; death 2 yrs. later apparently of bronchopneumonia; autopsy showed *no evidence of disease in chest wall or axilla, but many metastases in rt. lung*
26. Schuler 1895 (43; 68)	F adult	inoperable carcinoma	untreated	none	extensive abscesses in tumor area, fever for 18 days; 25 cc pus drained	*complete regression*; disease later recurred; end result unknown, probably died
27. Korff 1897 (68)	F adult	very extensive inoperable carcinoma breast and chest wall of enormous dimensions (14 yrs. duration)	not recorded	none	acute erysipelas, fever to 41.5°C	*extensive absorption of necrotic tumor tissue with very extensive phlegmon and acute sloughing of subcutaneous tissues, causing death*

PART II, SERIES A: INOPERABLE MAMMARY CANCER WITH CONCURRENT PYOGENIC INFECTIONS, INFLAMMATION OR FEVER, (cont'd)

Physician, Date References	Sex Age	Diagnosis Extent Disease	Treatment Prior to Infection	Subsequent Treatment	Type of Infection	Immediate and Final Results
28. Williams 1898 (68; 112)	F 45	scirrhus carcinoma lt. breast with axillary metastases	untreated, (mastectomy had been planned)	none	erysipelas involving lt. breast	*"diseased breast sloughed clean away leaving healthy granulating surface which rapidly cicatrized"*; no local recurrence; axillary metastases spread rapidly, death soon afterwards "internal dissemination."
29. Pearce & Gould 1902 (68; 79; 80)	F 41	recurrent inoperable carcinoma breast; multiple skeletal and soft part metastases including liver, also ascites (developed after castration) pathologic fracture of femur; condition terminal	radical mastectomy, bilateral oophorectomy, salpingectomy	none	developed pus-distended fallopian tubes 4 mos. after mastectomy; sinus in abdominal incision discharged for almost 3 yrs.	*subcutaneous nodule, enlarged liver, ascites all slowly subsided; neck of femur healed; NED for several yrs.*
30. Coley & Boomer 1905 (68)	F adult	terminal carcinoma of breast involving about 18 × 20 cm. of chest wall; entered hospital to die	probably untreated	none	violent erysipelas	*enormous tumor disappeared in 6 wks.; no recurrence; NED 9 yrs. later*
31. Strandgaard 1914 (9; 68; 95)	F 69	twice recurrent inoperable ulcerated adenocarcinoma lt. breast, strong suspicion of pulmonary metastases, involvement of rt. breast; weak heart	radical mastectomy 10½ mos. later recurrent nodules excised; 4 mos. later several suspicious areas in scar, as well as in lungs; some x-ray given	none	severe erysipelas 2 wks. after x-ray	*recurrent nodules disappeared; no further recurrence* 5 mos. later; died myocarditis and bronchopneumonia 6 mos. after erysipelas, 11 yrs. after onset
32. Marsh 1938 (9; 68)	F 54	inoperable carcinoma breast, multiple metastases to scalp;	biopsy; 400 mch radium	Coley toxins begun about 4 mos. after erysipelas, 9	facial erysipelas	*remarkable healing of scalp lesions, after erysi-*

		(disease spread rapidly after radium); prognosis "few months"		i.m. in arms; 2nd series 4 mos. later		*pelas*; no change after toxin injections; death about 15 mos. after erysipelas (survival prolonged?)
33. Ross-Loos 1959 (9; 68)	F 28	infiltrating duct carcinoma lt. breast extensive skeletal metastases to lumbar spine, sacrum, ribs, pelvis, rt. leg, pathologic fracture femur (onset during 3rd pregnancy in 4 yrs.) bedridden due to severe back pain, sciatica; chronic neurogenic bladder, bowel function affected	radical mastectomy 2 mos. after onset; x-ray (12,000 r); vitamin injections for back pains due to metastases caused temporary cessation of pain; testosterone; fracture pinned; bilateral oophorectomy, little benefit	polymyxin, gantrisin, x-ray to spine for 4 days, pain worse	cold, pyelonephritis (Pseudomonas aeruginosa); leukocytosis (11,500) acutely ill with fever; further fever, 2 more attacks pyelonephritis	*during each of 3 febrile episodes (pyelonephritis) back pain disappeared; after 3rd episode gained 25–30 lbs.*; disease reactivated, death over 4½ yrs. after onset
34. Pamard 1882 (68; 78a; or 79)	F adult	enormous encephaloid tumor of breast	?	?	erysipelas	*"in 15 days tumor melted away leaving granulating wound 5 × 6 cm in diameter which seemed to be healing"*; growth then again increased in size causing death
35. Kutzner 1889 (46; 68)	F 18	round cell sarcoma of breast, multiple metastases in subcutaneous tissues	?	?	acute pulmonary infection (pneumonia?)	*all evidence of disease regressed completely*; end result unknown

*This case had both a spontaneous and induced infection.

PART II, SERIES B:
INOPERABLE MAMMARY CANCER WITH NON-PYOGENIC INFECTIONS: 7 CASES

Physician, Date References	Sex Age	Diagnosis Extent Disease	Treatment Prior to Infection	Subsequent Treatment	Type of Infection	Immediate and Final Results
1. Trnka 1775 (14; 68; 103)	F adult	inoperable scirrhus carcinoma lt. breast; metastases much later involving entire rt. breast	lt. mastectomy; mercury internally and externally; no benefit	none	double tertian malaria	*within a few weeks after malaria developed complete regression of recurrent carcinoma*; end result unknown
2. Auzias-Turenne & Didot 1852 (16; 68)	F 30	3 times recurrent cancer lt. breast with apparent axillary metastases (nodular, very hard); condition regarded as hopeless	3 operations; 3rd recurrence developed shortly after 3rd operation, was untreated	prolonged mercurial treatment	''drowned her sorrows in promiscuous debauchery''; developed syphilis	*syphilis ''cured her cancer''* (regression occurred before mercurials were given); alive and well several yrs. later; NED
3. Paget 1853 (68; 78)	F 25	inoperable scirrhus carcinoma with axillary metastases, of very rapid growth, recurrent in skin about scar 6 mos. after mastectomy, extensive ulceration, frequent hemorrhages	mastectomy 3 mos. after onset; recurrence	none	12 mos. after recurrence appeared developed pulmonary tuberculosis	*carcinomatous ulcer then began to heal, axillary metastases almost entirely regressed over 6 month period,* but patient lost weight and strength, died 12 mos. after onset; autopsy: extensive pulmonary tuberculosis, liver metastases (none in lungs), one hard metastatic lymph node in axilla, low nodular mass in scar
4. Sibley & Laurence 1858 (48; 68)	F adult	ulcerated inoperable scirrhus carcinoma breast ''size of 2 oranges'' of 6 yrs. duration	?	none	concurrent pulmonary tuberculosis; bronchitis, pleurisy	*almost complete sloughing of tumor leaving healthy ulcer which later completely healed*; soon recurrence appeared below scar, *which diminished after bronchitis and pleurisy set*

						in; lung-symptoms increased; death due to tuberculosis (autopsy)
5. Sigg 1891 (68; 94)	F 33	3 times recurrent inoperable adenocarcinoma lt. breast 2 yrs. duration, involving skin, subcutaneous tissue over wide area around scars: "cancer-en-cuirasse" sternum to scapula and lt. arm, axillary metastases; tremendous weight loss	3 operations	none	severe pulmonary tuberculosis	*rapid decrease of extensive "cancer en cuirasse"; axillary mass reduced from size of fist to size of nut; entire area completely regressed* some days prior to death from tuberculosis; pathologist reported remains of axillary metastases contained a "yellowish emulsion"
6. Muller & Strauss 1926 (68; 96)	F adult	inoperable breast carcinoma	?	?	typhus	*complete healing*; end result unknown
7. Chardot 1962 (10a; 68)	F adult	bilateral breast carcinoma, with thoracic infiltrations, multiple bone metastases and a liver mass discovered at adrenalectomy	oophorectomy, adrenalectomy	?	hepatitis	*liver tumor disappeared*; survived 2 yrs. in good general condition

PART II, SERIES C: INOPERABLE MAMMARY CANCER WITH EXTENSIVE INFLAMMATORY EXUDATES (SPONTANEOUS OR INJECTED): 7 CASES

Physician, Date References	Sex Age	Diagnosis Extent Disease	Treatment Prior to Infection	Subsequent Treatment	Type of Infection	Immediate and Final Results
1. Vulpian 1885 (68; 108)	F 22	ulcerated inoperable scirrhus carcinoma lt. breast involving rt. breast adherent to chest wall and skin; metastases to both axillae, also to lt. supraclavicular, and cervical lymph nodes, abdominal wall; hepatomegaly; dry cough, advanced cachexia, prognosis extremely grave; severe abdominal pains; insomnia; edema of arm, ankles	tonics prescribed	?	slight peritoneal effusion, also hemorrhagic pleurisy (1–1½ litres)	4 wks. after effusions developed regression began, *edema and ascites subsided, regained appetite and strength, almost complete regression of primary and metastases*; at base of rt. lung there persisted a marked dullness, voice little resonant; end result unknown
2. MacKay 1907 (68; 54; 87)	F 39	recurrent inoperable scirrhus carcinoma with extensive metastases to sternum, supraclavicular region and lungs, involving whole chest; irritating cough (pressure on laryngeal nerve); almost moribund; morphia required for pain (1¼ gr.)	radical mastectomy (axilla involved); metastases 14 mos. later in scar below clavicle, with bulging of sternum; x-ray caused some retardation of growth rate	none	hemorrhagic pleurisy, with absorption of thoracic exudate	in grave condition for 6 wks., then *remarkable improvement, most marked in areas which had not been irradiated, apparently complete regression, pain ceased*; death 14 wks. after regression, of exhaustion, clinically NED at death, no autopsy
3. Tuffier 1910 (68; 104)	F adult	inoperable twice recurrent "cancer en cuirasse" involving chest wall and axilla with extensive ulceration, enormous edema of arm; cachexia	2 operations: 1895, 1897	sodium cacodylate for 7 mos.	hemorrhagic pleurisy (2 litres)	*ulcerated area healed, metastases regressed; gained weight and strength; NED over 6 yrs.* after onset and first surgery

4. Hodenpyl 1910 (41; 53; 68)	F 37	recurrent carcinoma of breast (multiple), extensive liver metastases nearly filling abdomen, others on neck, breast; general health deteriorated; prognosis very grave, terminal	radical mastectomy followed by rapid recurrences which were removed, others soon followed on neck and breast	?	October 1906; extensive chyliform ascites, persisted for 4 yrs. requiring frequent tapping	*condition improved, tumors in neck, breast gradually decreased, then disappeared, abdominal masses imperceptible, liver smoother, emaciation decreased*; extreme chyliform ascites persisted, no other evidence of disease; end result unknown
5. Tuffier 1910 (68; 104)	F 37 actress	recurrent inoperable far advanced "cancer en cuirasse" primary in rt. breast; enormous edema of arm and hand 18 mos. after surgery; entire rt. chest, axilla to sternum surrounded by cutaneous nodules; intense pain causing insomnia	mastectomy 18 mos. prior to pleurisy	Tuffier aspirated 400 cc of pleural exudate centrifuged it, injected 20 cc subcut. every 5 days caused febrile reactions of 39°C; repeated injections nucleinate of soda for 3 wks., febrile reactions 39.5°–40°C	pleurisy, rt. chest pain under spine of rt. scapula, rapid respiration; subsided after 4th injection of exudate	*edema of arm markedly diminished, general condition much improved; by end of fever therapy edema of arm gone, no pain, large indurated placque on chest progressively softer leaving only slight thickening of skin, not adherent to deeper tissues; apparent cure*; returned to stage, NED 3 yrs. later, 4½ yrs. after onset
6. Nohrman 1950 (76; 87)	F 46	inoperable multiple metastases, scirrhus breast adenocarcinoma, parietal pleura, diaphragm, lung, biopsy of lung lesion positive 1942	onset April 1935; pre- and post-operative radiation November 1935; radical lt. mastectomy for lesion 4×5 cm., skin adherent; March 1937, simple rt. mastectomy (fibroadenomatosis); well 6½ yrs.	January 1944 130 cc dark fluid evacuated, thoracoscopy; great many metastases present 1947; x-ray to axilla, then axillary dissection	December 1943: rt. pleural effusion	early 1944, exudate cleared in 2 mos., *complete regression all metastases; well 3½ yrs.* after thoracoscopy; 1947, rt. axillary node enlarged; never fully recovered from axillary surgery; metastases to ventricle and liver, death September 1948, 13½ yrs. after onset; autopsy showed calcification, induration of connective tissue, metastases present in pleurae, liver, omentum, mesentery and ovaries

PART II, SERIES C: INOPERABLE MAMMARY CANCER WITH EXTENSIVE INFLAMMATORY EXUDATES (SPONTANEOUS OR INJECTED), (cont'd)

Physician, Date References	Sex Age	Diagnosis Extent Disease	Treatment Prior to Infection	Subsequent Treatment	Type of Infection	Immediate and Final Results
7. Ross et al 1982 (76; 87)	F 60	early 1973: inoperable adenocarcinoma lt. breast 6.5 × 6.5 cm., skin fixation, nipple retraction, peau d'orange, axillary, supraclavicular node metastases; September 1973 metastases lt. pleura, 8th, 9th rib	January 1973: radiation to lt. breast & nodes (5000 rads); primary, supraclavicular node regressed, axillary nodes decreased	no treatment for 1st effusion; 1980: an antiestrogen given, (no benefit); tamoxifen then caused decrease in effusion; carcinoembryonic antigen (CEA) declined from 33.4 to 13.4 ng/ml in 8 mos. Tamoxifen continued to August 1981; thoracentesis, resection chest wall disease; aminoglutethimide	September 1973: lt. pleural effusion yielded 150 ml. at thoracentesis; February 1980, again had pleural effusion showing adenocarcinoma cells. Further pleural effusion recurred 1981–82	complete regression all lesions by January 1974; NED until 1980 but CEA gradually rose from normal 4.1 ng/ml. in May 1978 to 46.9 ng/ml. in February 1980; remained stable on tamoxifen until August 1981; refused systemic chemotherapy; rapid downhill course with ascites; death April 8, 1982, 10 yrs. after onset

PART II, SERIES C: INOPERABLE MAMMARY CANCER WITH INFLAMMATORY EXUDATES SELECTED DETAILED HISTORIES

CASE 2: Recurrent inoperable scirrhus carcinoma of the breast with the metastases in the sternum, supraclavicular region and lungs, confirmed by clinical and microscopic examinations of the primary growth and of some of the metastatic lymph nodes, at the Deaconess Hospital, Edinburgh, Scotland.

PREVIOUS HISTORY: Female, age 39. Onset, in April 1904 she first noted a lump in her right breast. She was first seen by Dr. Charles Gordon MacKay, of Lochcarron, Scotland, in October 1904, at which time she had a typical mammary scirrhus. The diagnosis was confirmed by Dr. Bruce of Dingwall, and the patient was admitted to the Deaconess Hospital of Edinburgh in November 1904. She appeared to be in very good health. Examination on admission showed a circumscribed cancer in the outer quadrant of the right breast, adherent to the skin, but no lymph nodes were palpable in the axilla.

SURGERY: A radical mastectomy was performed on November 4, 1904. The axillary nodes were involved, but the prognosis did not seem particularly unfavorable.

CLINICAL COURSE: The patient made a good recovery and went home. On January 9, 1906, 14 months later, she returned with small fixed recurrent nodules in the scar, a larger one below the clavicle, and a bulging of the sternum.

RADIATION: As the condition was completely inoperable, the patient was given x-ray therapy to the point of producing reddening and scaling of the skin. The progress of the disease appeared to be arrested. In August 1906 she returned for another course of x-ray therapy. In the interim the disease had progressed and there was an irritating cough, apparently due to the pressure of the metastases on the laryngeal nerve.

CONCURRENT INFLAMMATION: There was marked dyspnea and dullness over the pleural cavity on both sides. Thoracentesis yielded 40 oz. of blood-stained fluid from the left pleural cavity, and 10 oz. from the right. After thoracentesis there was dullness up to the lower angle of the scapula on both sides, and there was also dullness of the right apex. A fortnight later 28 oz. of bloodstained fluid were aspirated from the left pleura. The dyspnea returned. An attempt was again made to tap the left pleural cavity but only a few ounces were withdrawn. It was inferred that the dullness was mostly due to the thickening of the pleura and consolidation of the lung, due to metastases. The patient gradually failed, and made up her mind to go home. She was discharged on November 8, 1906, in a hopeless condition. For several weeks in December she was in a state of semi-collapse. At this time there was a deep blue discoloration over the whole front of the chest from the clavicles to a line a little above the upper margin of the liver. The left breast was of great size and hard. The left axilla was obliterated, filled with malignant growth, and the right axilla was almost filled. Both sides of the chest contained fluid almost to the clavicles, respiration being 44. Swallowing anything, even a teaspoon of water, was difficult, and at times impossible. This state continued up to December 28, 1906. The next morning the condition had entirely altered. The patient was much better and felt comparatively comfortable. She could swallow easily. The respiration had fallen from 44 to 24. The fluid in the chest had practically gone. She gradually took food in greater quantity and improved in every way. Still more remarkable was the fact that the

seat of the local disease (the pectoral region) gradually underwent a change for the better quite as great as the general condition. In its whole extent the deep purple discoloration gradually become markedly lighter. In some places the skin regained its normal whiteness, and where it had been tense and shining it became at first wrinkled, then flaccid.

It was noted that the diseased parts which had *not* received x-ray therapy, had undergone an extraordinary change: the left breast which had grown to a large size and felt hard, had absolutely disappeared with the exception of a brownish-yellow circular flat disk the size of a sixpence, of horny consistency and appearance, which occupied the place where the nipple had been. There was absolutely no trace of the mammary gland and where it had been the skin was flat and close to the ribs. The left axilla which had been full of metastases was now a cavity into which MacKay could place his closed hand. The right axilla was the same. In the space where the right breast had been excised and the parts adjacent had all been subjected repeatedly to x-ray therapy the improvement, though quite as great, had gone on at a slower pace. MacKay stated: "Though there is healthy action, the tissues seem to be in a semi-paralysed state. The x-ray had not been elective in action. It had affected the disease and the healthy tissues in equal degree."(54)

CLINICAL COURSE: The cough, which had never been absent for ten months, ceased completely on January 6, 1907, and had not recurred when the case was reported in July 1907. The steady improvement continued in every way. Morphine, which had been administered steadily for some time in 1¼ grain doses, was stopped altogether by February 1907.

In reporting this case, MacKay stated that the patient had been in a half-starving, dehydrated condition, a state most favorable to the absorption of the thoracic exudate. When the absorption took place, the pressure on the esophagus was relieved, so that swallowing became possible, as well as relieving the lungs, so that respiration fell to 24. However, the improvement, not only general but also local, coincided exactly in point of time with the disappearance of fluid from the chest . . . the fluid (serum) had been suddenly, rapidly and in considerable quantity taken into the system. It thus came into contact with a malignant growth which at that moment was overwhelmingly master of the situation. The growth then not only ceased to advance but actually withered. McKay believed that a powerful agent in the *serum* had produced this result. He suggested that patients might be artificially "inoculated" with such a serum. In conclusion he stated that he felt that the victory over cancer will ultimately be through a serum.(54)

In a personal letter to H. Gideon Wells, M.D., of Chicago, MacKay stated: "I described the changes as if the tumors had withered. A closer description would be that it looked as if the tumors had dissolved, and so dissolved as to become absorbed, leaving nothing but the covering of skin." Wells was much impressed with this case and he stated: "Apparently the serum from the cancerous pleura on being absorbed, either itself or else, which seems to be more probable, it stimulated the resisting powers of the organism and led to the development of cytolysins for the cancer cells, which caused the rapid retrogression of the cancer tissue."(111)

MacKay informed Wells that this patient died some five weeks after he had read his paper, or about 14 weeks after the disease had regressed. MacKay added: "She had gone through a very great amount of suffering under circumstances of excessive mental strain, and she died of exhaustion. So far as we could make out clinically the disease had absolutely left her. Whether if she had lived it would have recurred, is another matter."(111)

In reporting this case MacKay further stated: "There can be little doubt that occasionally a true cancerous tumor comes to a pause in its growth, when it seems in fact to have lost

its power of further attack on healthy tissue, and then a cure, more or less complete, is said to have taken place. When this has happened it is reasonable to suppose that some agent must have been at work either as aiding the body tissues in their resistance to attack, or acting in antagonism to the cancer cell, and so diminishing its invasive vigour. If there be any such active agent, what is it? Is there possibly elaborated in the body of the patient a something which can act in this way and so effect a spontaneous cure?'' He believed the above case ''seemed to suggest an answer to this question.''(54)

COMMENT: It is now known that inflammatory exudates kill cancer cells *in vitro* as well as *in vivo*.

> **CASE 3:** Recurrent inoperable far-advanced ''cancer en cuirasse'', with extensive edema of the entire arm, confirmed by repeated histological examinations made during the course of treatment.

PREVIOUS HISTORY: Female, age 37, actress. The family and previous personal history were not recorded. Onset, the patient developed cancer of the right breast.

SURGERY: A mastectomy was performed in January 1908.

CLINICAL COURSE: She consulted Dr. Theodore Tuffier, of Paris, France, 18 months later and was admitted to the hospital on June 21, 1909. At this time she was very thin, with a yellowish pallor, and the right arm was enormous—''a veritable elephantiasis''. For two months she had been unable to move it because of the edema which extended to the fingertips. The axilla and the supraclavicular region were indurated, and there was an enormous scirrhus ''cancer en cuirasse'' occupying the entire right mammary region and extending from the axilla to the sternum—the entire mass surrounded by cutaneous neoplastic nodules. The patient suffered intense pain in the arm, causing insomnia.

CONCURRENT INFECTION: She had recently developed pleurisy involving the right chest and causing pain under the spine of the left scapula and rapid respiration. Tuffier believed that ''if there exists a cancer antibody, the surest place to find it would be in the pleuritic effusion of a cancer patient''. He felt justified in trying this out on this patient.

INJECTIONS OF PLEURAL EXUDATE: Tuffier therefore withdrew 400 cc. of the pleural exudate, cleansed it by centrifuging and injected 20 cc. of this liquid material subcutaneously every fifth day. These injections caused febrile reactions of 39°C. (102.2°F.). After the fourth injection the pleural effusion disappeared, the edema had markedly diminished and the general condition of the patient was much improved.

ARTIFICIAL FEVER THERAPY: On the basis of this observation Tuffier considered himself justified in trying a more drastic technic. He therefore injected nucleinate of soda subcutaneously, determining the dose empirically at 0.75 to 1 gram so as to produce a temperature of 39.5° to 40°C. (103.1°–104°F.) on the evening of the day an injection was given. He repeated the dose whenever the fever dropped to 38°C. (100.4°F.). In this way the patient was kept febrile continuously for three weeks. At the end of this period *the edema of the arm had entirely disappeared, the pain had ceased, and the large indurated plaque had become progressively softer,* leaving only a slight thickening of the skin which was not adherent to the deeper structures.

CLINICAL COURSE: Eventually the patient left the hospital apparently cured, and a year later sent word she was back on the stage. This was about three years after onset.(104)

In reporting this case in 1910 Tuffier stated: ''The improvements were followed by all the students and visitors to my service, and were so marked that I might have found it

difficult to believe we were dealing with a case of cancer, if several histological examinations had not been made during the course of the treatment." He added: "This result does not surprise me, for 30 years we have known how much *injections which cause febrile reactions are capable of ameliorating cancer*. My master, Verneuil, often used to speak of this to us."(106)

Meyer, in reporting this case, added: "*Tuffier never saw a similar result in other cancer patients that were treated in the same way*."(59a) Is it possible that in none of the other patients was there an initial pleurisy, followed by injection of pleuritic infusion; that both were necessary to envoke a complete regression?

Meyer went on to say in regard to patients developing immunity to various injected materials: "And here it is where the difficulty with this kind of treatment seems to be. In the experience of Tuffier, Bier and others, by whatever kind of injections the first strong reactions had been obtained, the system of the patient soon becomes tolerant to the injected substance, and the force of the substance is exhausted before the tumor has been healed. If now another serum or solution of some kind is employed, it may still ameliorate the cancerous condition, but less than the first one and its force will sooner become exhausted; a third still more so and eventually a change of serum will have no further effect at all.

"Postulated therefore is a serum of such range of dosage, without bad side-effects, that the tolerance can be overcome by increases of the injected dose, and that in this way the patient can be kept, and without fail and without interruption, in a long continued state of fever.

"Such a serum seems to be Coley's Fluid."(59a;68;104)

PART II, SERIES D:
OPERABLE MAMMARY CANCER WITH PYOGENIC INFECTION:
15 cases (14 accidental, 1 induced)

Physician, Data References	Sex Age	Diagnosis Extent Disease	Treatment Prior to Infection	Subsequent Treatment	Type of Infection	Immediate and Final Results
1. Collins 1864 (13a; 68)	F 42	scirrhus carcinoma lt. breast size of orange	leeches; mercurial plasters, no effect; mastectomy	none	erysipelas 6 days after surgery involving whole chest; phlebitic inflammation lt. eye, photophobia, severe pain; condition grave	lost sight of lt. eye; *recovered, no recurrence*, but slight cervical lymphadenopathy 3 yrs. later, about 3½ yrs. after onset, end result unknown
2. Mosengeil 1871 (62; 68)	F 40	carcinoma rt. breast, very rapid growth, axillary metastases (mother and sister had died of carcinoma)	mastectomy, including excision of some of the smaller lymph node metastases	none	erysipelas 4 days after surgery in lower edge of wound, lasting 5 days; 24 hrs. later fresh attack extending over whole back from neck to gluteal region and anterior thorax lasting 11 days	*wound healed rapidly, complete recovery NED 18 mos. later;* end result unknown
3. Czerny 1895 (14; 68)	F adult	carcinoma breast recurrent 1 yr. after surgery (numerous hard subcutaneous nodules)	radical mastectomy; recurrent nodules removed surgically	none	erysipelas (moderately severe) in region of wound from 2nd operation	*complete recovery, NED 20 yrs. later*
4. Coley 1896 (68)	F adult	advanced carcinoma of breast	mastectomy	none	erysipelas developed during wound healing	*complete recovery NED 5 yrs. after surgery*
5. Coley 1896 (68)	F adult	advanced breast carcinoma	mastectomy	none	erysipelas during wound healing	*complete recovery traced well over 5 yrs., NED*
6. Coley 1896 (68)	F adult	advanced breast carcinoma	mastectomy	none	erysipelas during wound healing	*complete recovery traced well 15 yrs., NED*

PART II, SERIES D: OPERABLE MAMMARY CANCER WITH PYOGENIC INFECTION, (cont'd)

Physician, Data References	Sex Age	Diagnosis Extent Disease	Treatment Prior to Infection	Subsequent Treatment	Type of Infection	Immediate and Final Results
7. Lomer 1903 (52; 68)	F adult	carcinoma of lt. breast	mastectomy		wound suppurated freely discharging much pus; 5 yrs. later pneumonia (fatal)	*NED for 5 yrs.*, then metastases in lt. axilla; pneumonia caused death over 5 yrs. after onset; autopsy: cells in axillary metastases very small, no mitoses; *Lomer attributed delayed metastases to suppuration, other changes to pneumonia*
8. Coley 1905 (11; 68)	F adult	extensive breast carcinoma	involved area removed surgically	none	severe erysipelas during wound healing	*alive and well 5 yrs. later, NED*
9. Elting ? (9; 68)	F early 30's	extensive breast carcinoma with widespread ulceration	radical mastectomy with resection of several ribs	none	violent postoperative wound infection, erysipelatous type	*alive and well 30 yrs. later, NED*
10. Mayo Clinic 1921 (9; 68)	F 48	carcinoma rt. breast, grade 3, axillary metastases (many cases cancer in family); also had toxic thyroid adenoma; (injured breast 6 mos. prior to onset)	rt. radical mastectomy 1 mo. after onset	none	staph infection in wound, suppuration for 2 mos., febrile for 2 days	after recovery thyroid condition flared up requiring thyroidectomy 3 mos. after breast surgery; *NED*; much later crippling arthritis; bladder carcinoma caused death 1960, 40 yrs. after onset of breast carcinoma
11. Lindenstein 1930 (50; 680	F 45	breast carcinoma	radical mastectomy; postoperative radiation	x-ray after 2nd erysipelas caused regression; further x-ray after 3rd erysipelas again caused some regression of sternal mass, no effect on lung	3½ yrs. after mastectomy erysipelas infection over area of former tumor and in back (not severe); wet compresses applied easy recovery; 2nd erysipelas 6	*NED for 38 mos. after erysipelas*, then recurrence over sternum size of walnut; began to regress after x-ray; then rapid increase in size; no effect from 3rd

				lesions; 20 cc pleural exudate injected in gluteal muscles (no effect)	mos. after 1st; 3rd erysipelas 5 mos.	erysipelas; extensive pleural, pulmonary metastases; no effect from pleural exudate; death 7 yrs. after onset
12. Morton 1953 (9; 68)	F 55	carcinoma rt. breast	excisional biopsy about 5 wks. after onset; 2 wks. later radical mastectomy; x-ray (5000r)	metastases biopsied; given x-ray responded very well	due to infection wound took 4 mos. to heal	slight edema rt. arm, NED 16 yrs.; ulceration developed in rt. axilla, several crusted nodules over anterior rt. shoulder; disease progressed, death; widespread metastases 20 yrs. after onset, at 75
13. Coley & Neale 1893 (12; 68)	F 36	spindle cell sarcoma breast	mastectomy	none	erysipelas post-operatively	NED, 5½ yrs. after infection
14. Matagne 1905 (57; 68)	F adult	carcinoma breast	none	mastectomy 3 mos. after infection	attenuated cultures streptococcus injected subcut. or i.m. in back, producing painful inflammatory indurations, several of the 8 sites developed furuncles and had to be incised	NED 3 yrs. later
15. Montgomery 1961 (9)	F 61	bilateral scirrhus adenocarcinoma, with 2 metastases to low lymph nodes left axilla; 10 lb. weight loss; onset January 1961 panhysterectomy January 1958 for menorrhagia, severe anemia; premarin given 21 days a month; patient very tense; mother died breast cancer; heavy smoker	bilateral radical mastectomy January 25, 1961	drainage of wound, penicillin, mancomycin; further antibiotics for cellulitis, hospitalized about 5 wks.; October 1961 halotestin (not well tolerated) then Stilbesterol increased to 25 mgs. daily; July 1966, chemotherapy: 5FU leukoran & cytosine arabi-	February 7, 1961 abscess in rt. breast area (Staph. aureus) fever to 104°F.; cellulitis of lt. breast incision; hemolytic strep. & Staph. aureus; December 1966 developed an acute cold	regained weight slowly, appetite poor, very tense; *well 4 yrs.*; October 1965: 3 recurrent nodules on lt. breast area several metastases rt. lung; skin and lung lesions regressed moderately on endocrine therapy; May 1966 metastases to ribs bilaterally: lung fields clear except for

PART II, SERIES D: OPERABLE MAMMARY CANCER WITH PYOGENIC INFECTION, (cont'd)

Physician, Data References	Sex Age	Diagnosis Extent Disease	Treatment Prior to Infection	Subsequent Treatment	Type of Infection	Immediate and Final Results
				noside (well tolerated); June 1967: 2 transfusions, excellent effect; given isoniazid June 1968 for supposed t.b.		minor pleural thickening; continued to live her usual life; rib & skin lesions then became more prominent, regressed markedly under chemotherapy; multiple rib densities recurred after her cold but lung fields cleared; continued to be active but weight declined to 86 lbs. by March 1968; *suspected of having pulmonary t.b.*; disease progressed; dyspnea, bone, pleural & mediastinal involvement; death August 28, 1968, 7½ yrs. after onset

PART II, SERIES D: OPERABLE MAMMARY CANCER WITH PYOGENIC INFECTION SELECTED DETAILED HISTORY

CASE 14: An untreatable operable mammary carcinoma, received inoculations of living streptococcal cultures. As Dr. Henri Matagne had already treated several cases of inoperable neoplasms with injections of nonsterilized cultures of streptococcus, this operable case was referred to him for pre-operative toxin therapy. He considered it safe to use very old attenuated cultures without sterilizing them, believing that these would yield a more effective preparation. As this patient was a very impressionable woman he decided not to make any local injections (his usual technique). He therefore made eight injections on her back (subcutaneous or intramuscular). Each one caused a painful, inflammatory induration and in these areas furuncles developed, several of which had to be incised.

The patient refused further treatment and three months later a mastectomy was performed.

There was no recurrence or metastases and the patient remained well when Matagne reported the case in 1905. At this time he stated it was of particular interest because he thought the 'accident' which supervened (i.e. the furuncles), saved the patient, because he could not imagine that eight injections could produce immunity in the space of three months, while he could easily understand that the large quantity of streptococcus toxins produced in the patient's organism could produce the same beneficial effects normally achieved by a regular course of Coley's toxins. He added: "I therefore consider that I am justified in attributing the cure to the toxin treatment. Thereafter, however, I always took care to use only sterilized toxins."(57)

Matagne continued to use this method successfully for many years, and published several more papers on the subject, the last two being in 1951 and 1953. (These references appear after Part III.)

PART II, SERIES E:
INOPERABLE MAMMARY CANCER INOCULATED WITH STREPTOCOCCAL CULTURES: ERYSIPELAS DEVELOPED IN 8 OF 11 CASES

Physician, Date References	Sex Age	Diagnosis Extent Disease	Treatment Prior to Inoculations	Subsequent Treatment	Type, Extent and Duration of Infection	Immediate and Final Results
1. Fehleisen 1886 (27; 68)	F 49	3 times recurrent breast carcinoma; hemispherical mass 5–6 cm. in diameter in cicatrix, firmly adherent, several satellite nodules	3 operations; further surgery refused for final recurrence, but readily consented to inoculations	none	pure cultures streptococcus erysipelatis (9th generation) inoculated in 5 places in tumor area; caused fever 38°C; erysipelas over entire rt. thorax to posterior axillary line, in 4 days spread from sternum to vertebrae, slight pleural effusion; severe headache; 2nd attack erysipelas spread over entire thorax to umbilicus	*within 5 days largest tumors regressed 50%, smaller ones no longer palpable; complete regression in 9 days, skin perfectly flat: "therapeutic effect perfect"; NED 2 yrs. later,* 4 yrs. after onset
2. Fehleisen 1896 (27; 68)	F 51	advanced carcinoma, rt. breast size of 2 fists with large axillary metastases, also numerous satellite nodules extending to distal half of scapula	silver nitrate applied in a circle to see if erysipelas could be limited	pleural effusion; aspirated twice (dyspnea)	pure cultures of strep (15th generation) inoculated; 6 small scarifications rubbed in; all took; 19 hrs. later severe chill; erysipelas spread over whole breast to scapula then to shoulder and proximal rt. arm; no fever	*largest mass regressed markedly in 4 days, 50% in 15 days; 8 nodules disappeared, 5 remained;* no further regression; end result unknown
3. Fehleisen 1896 (27; 68)	F 40	twice recurrent carcinoma of breast inoperable axillary and cervical metastases; (of 6 yrs. duration)	3 operations	incision and drainage of 10 cc necrotic tumor tissue	pure cultures of strep (17th generation) inoculated; 15 hrs. later chills, fever 39.6°C for 11 days; infection spread over whole anterior thorax, over shoulder to spine, down arm to hand	*9 days later one metastasis was soft, fluctuating, 3 days after incision and drainage healing occurred;* no further regression; end result unknown

4. Janicke & Neisser 1884 (44; 68)	F 40	recurrent inoperable breast carcinoma of very rapid growth involving pectoral and axillary regions, edema of arm, unbearable pain	primary tumor removed surgically; recurrence 3 mos. later	none	strep culture obtained from Fehleisen, rubbed into overlying skin after scarification causing very severe erysipelas, fatal on 4th day	*in 4 days tumor much softer, regressed, overlying skin wrinkled*; autopsy: *"carcinoma nests appeared to have been destroyed by direct action of the streptococci" almost complete regression had occurred*
5. Feilchenfeld 1888 (28; 68)	F adult	very far advanced scirrhus carcinoma breast of slow growth with extensive involvement axillary, cervical and clavicular lymph nodes	primary tumor removed surgically	none	strep culture inoculated resulting in severe erysipelas extending over entire trunk and down arm, causing death	*neoplasm not essentially influenced by the infection*
6. Holst 1888 (41a; 68)	F 40	infiltrating, inoperable, ulcerated carcinoma rt. breast, recurrent a few mos. after mastectomy involving entire rt. chest, infiltrating nodular growth with satellite nodules	mastectomy	none	inoculations of attenuated cultures proved ineffective fresh cultures from Fehleisen caused erysipelas infection over entire lt. chest and back, high fever for about 7 days; erysipelas recurred (mild, chronic form)	*entire ulcerated area regressed within 6 wks.*, 2 wks. later disease reactivated, ulceration recurred, further metastases along arm where it had rested on ulcerated area; *no apparent effect from mild, recurrent infection*; general condition failed, appetite decreased; end result not recorded, probably death
7. Coley 1893 (12; p. 495; 68)	F 40	3 times recurrent carcinoma lt. breast 13 × 10 cm., markedly protuberant ulcerated, profuse discharge; metastasis size of egg in rt. breast, adherent to skin (of 18 mos. duration)	4 operations in less than a yr.	none	inoculations of living bouillion cultures of Streptococcus erysipelatis; begun August 1, 1892, continued at short intervals for 2 mos., moderate reactions lasting 24–48 hrs., but true attack did not occur.	*considerable regression, partial degeneration of tumor; general condition excellent*; after inoculations were stopped; tumors soon began to increase in size; end result unknown

PART II, SERIES E: MAMMARY CANCER INOCULATED WITH STREPTOCOCCUS CULTURES TO PRODUCE ERYSIPELAS, (cont'd)

Physician, Date References	Sex Age	Diagnosis Extent Disease	Treatment Prior to Inoculations	Subsequent Treatment	Type, Extent and Duration of Infection	Immediate and Final Results
8. Starr & Coley 1893 (12, case 34 in table; 68)	F adult	inoperable breast carcinoma with metastases to axillae and arm	?	?	severe attack erysipelas induced by direct inoculation from a fresh case; extended down arm and over breast	*axillary nodules entirely disappeared; improvement only temporary;* end result unknown
9. Finney & Coley (1893) (11; 12; 68)	F adult	recurrent inoperable carcinoma both breasts, intense pain, severe cough due to pleural involvement; internal metastases	morphine required almost constantly	morphine no longer needed, only a little codeine for cough	pure culture Strep. erysipelatis inoculated, but a true erysipelas was not induced	*pain almost disappeared after first reaction; palliative effect in this terminal case considered of great value;* died 3 mos. later of inanition
10. Coley 1894 (11; 68)	F 55	recurrent inoperable breast carcinoma	not recorded		inoculations of living cultures of Strep. erysipelatis; no erysipelas occurred; developed pleurisy	died 6 days later
11. Petruschky 1896–7 (68; 81)	F adult	inoperable recurrent cancer breast	mastectomy; recurrence untreated		inoculated 15 times with virulent culture Strep. erysipelatis; 4 showed no effect, 11 produced typical mild erysipelas lasting 4–5 days with fever; 10 cc anti-strep. serum also given (Marmorek), 24 hrs. prior to inoculations, but this never retarded development or lessened intensity of erysipelas	*marked regression or flattening of recurrent nodules;* end result unknown

PART II, SERIES E: INOPERABLE MAMMARY CANCER INOCULATED WITH STREPTOCOCCAL CULTURES. SELECTED DETAILED HISTORY

CASE 1: Female, age 49. The patient had had three operations for a carcinoma of the right breast, the last being on December 29, 1880. In the spring of 1881 a third recurrence developed in the cicatrix. She refused further surgery. She readily consented to being inoculated with streptococci. At this time there was a tumor 5 to 6 cm. in diameter in the cicatrix, firmly adherent to the reddened skin, as well as several small nodules the size of hazelnuts below and anterior to the larger growth.

INOCULATIONS: On September 15, 1882, at 11 a.m., the first inoculation was made with a culture of the ninth generation. Next morning the temperature was somewhat elevated (38°C.). There were no other symptoms until 5 p.m. when a rigor occurred. Half an hour later Fehleisen saw the patient and found that erysipelas had already spread over the whole tumor, reaching the size of the palm of the hand. Two days after the inoculation the erysipelas had spread over the whole right half of the thorax to the posterior axillary line. The pulse was frequent and sometimes intermittent, the headache was severe. That night the patient was disturbed, at times delirious. On the fourth day the infection had extended anteriorly as far as the sternum and posteriorly to the vertebrae. There was evidence of slight pleuritic effusion on the affected side. It was noted that the tumors had distinctly decreased in size. She had another restless night with severe headache. On the fifth day the larger growth had regressed 50 per cent (to 3.5 cm. in diameter) and the smaller ones were no longer palpable. On the seventh day respiration was difficult and the pleural effusion had reached to the lower angle of the scapula. The erysipelas had spread behind beyond the midline and in front had invaded the left breast. In some places vesicles formed. The pulse was small and intermittent. Camphor was ordered internally. Nine days after the inoculation the patient was free from fever and felt well. The redness was somewhat less marked. That evening the temperature again rose to 38.5C. It was noted that the recurrent tumors had all completely disappeared, and the skin lay perfectly flat on the ~~thorax~~, where formerly there had been a hemispherical swelling. At one point only in the cicatrix a hardness could be felt about the size of a pea. The erysipelas spread over the left breast and the left side of the back. By September 25, 10 days after the inoculation, the pleural effusion had been entirely absorbed, but the erysipelas broke out again over the right scapula, where it had previously entirely disappeared. It continued to spread and two days afterward reached to the umbilicus. The evening pulse was rapid and intermittent. Camphor was ordered internally. The infection subsided and after September there was no further fever.

Fehleisen, in reporting this case in 1886, stated: "The therapeutic result of this inoculation is up till now perfect, but whether it will remain so of course only can be determined by further observation." (27 Case 2, p. 274)

She remained well and free from further recurrence over six years after onset. DeWitt cited this case as a permanent result in 1895. The case was also cited by Feilchenfeld (28) and Coley (12).

PART II, SERIES F:
INOPERABLE MAMMARY CANCER PATIENTS IN WHOM INFECTIONS OTHER THAN STREP WERE INDUCED:
6 CASES

Physician, Date References	Sex Age	Diagnosis Extent Disease	Treatment Prior to Infection	Subsequent Treatment	Type, Extent and Duration of Infection	Immediate and Final Results
1. Amoureux 1752 (1; 68; 98)	F 36	extensive ulcerated breast cancer; overlying vessels varicose, nipple retracted; onset following suppression of menses after fall from horse; lancinating pain	?	none	"septic cataplasm applied: produced ulceration, slight fever, severe pains, vast deep ulcer, sternum to axilla; "laudable suppuration was established"	hemorrhages due to necrosis; *healing began following suppuration; complete regression in 4 wks.;* end result unknown
2. (Schwe[illegible])* cited by Dupré de Lisle 1774 (19; 68; 95, case 80)	F adult	recurrent inoperable breast carcinoma	surgery refused; venesection; leeches, emollient resolvent compresses; conium, hydrochlorate of gold orally, vegetarian diet	none	abscess on leg with suppuration; against advice patient allowed it to heal; new wound opened at site of former abscess causing further suppuration; "as abscess increased and suppuration became more abundant, breast cancer diminished until no trace remained"	*when suppuration again became well established, recurrent growth again gradually regressed;* end result unknown
3. Robert 1794 (68; 86, p. 155; 98)	F 37	extensive, far-advanced breast cancer, about 77 cm. in circumference, uneven, nodular, immovable, vessels varicose; lancinating pains, unable to sleep, exhausted	conium extract, & other remedies; then treated by a charlatan, causing rapid increase in size; surgery refused	none	small incision in center of breast, covered with dressings soaked in gangrenous discharges; gangrene developed, foul odor; in order to prevent recurrence 2 setons established before cure was complete	*rapid destruction of entire tumor mass in 18 days; 2 metastatic lymph nodes showed fatty degeneration containing a yellowish fluid; wound healed completely in 4 mos.; NED, entirely well 18 yrs. later*

*NOTE: This case had both a spontaneous and an induced infection.

4. Duparque 1839 (18; 68; 98)		hard nodular tumor of rt. breast, adherent to skin near nipple; prognosis very grave	surgery refused, venesection; leeches, emollient resolvent compresses; conium, hydroclorate of gold internally, vegetable diet		cautery applied to lt. arm, causing suppuration	*gradual regression for 6 mos., complete disappearance in 8 mos.*; end result unknown
5. Auzias-Turenne (Didot) 1851–52 (16; 17; 68)		hard nodular tumor in breast, lancinating pain (4 relatives died of cancer)	untreated	mercurial treatment begun a yr. later for the syphilis	inoculations of pus from syphilitic chancres made on back of neck, & 2 or 3 took, with symptoms of constitutional syphilis developing successively for a yr.	*complete recovery, in good health when reported a yr. or 2 later.*
6. Lomer (Nocht) 1903 (52; 68)		terminal breast carcinoma	not recorded		malaria was induced by inoculation of the blood of a tertian malaria patient; typical malarial fever occurred, & parasites were found in the patient's blood	*patient profoundly prostrated by the malaria; died soon after* malaria was arrested by quinine; autopsy revealed many metastases, especially in brain.

PART II, SERIES G:
INOPERABLE MAMMARY CANCERS IN WHICH GANGRENE DEVELOPED SPONTANEOUSLY OR BY INOCULATION: 10 CASES

Physician, Date References	Sex Age	Diagnosis Extent Disease	Treatment Prior to Gangrene	Subsequent Treatment	Extent of Gangrene	Immediate and Final Results
1. Le Dran 1741 (6; 68; 98)	F 15	very extensive inoperable cancer lt. breast, 8 yrs. duration, very hard, moderately painful, very dark red, beginning ulceration	none	none	gangrene developed; in 2 days entire tumor detached itself, sloughed off en masse during night, with profuse hemorrhage, leaving black almost circular wound 20 cm in diameter; suppuration followed	wound healed normally for 5 weeks., then recurrence in unhealed center portion disease progressed; death 7–8 mos. later.
2. Quesnay 1749 (68; 82; 113)	F adult	enormous ulcerated mammary carcinoma; overlying veins engorged	none	none	putrid suppuration, gangrene soon involved entire tumor	tumor became quite soft, almost painless; died septicemia
3. Amoureux 1760 (1; 68; 98)	F 36	extensive ulcerated mammary carcinoma overlying vessels varicose, nipple retracted, lancinating pain	septic cataplasm applied in order to produce suppuration	belladonna, herbs, venesection	vast deep ulcer developed, sternum to axilla, hemorrhages due to necrosis; laudable suppuration established	healing, complete cure in a month; not traced
4. Garneri 1810 (37; 68; 98, case 50)	F 59	inoperable far advanced ulcerated nodular scirrhus carcinoma, extensive, infiltrating axilla, involving entire lt. breast, lancinating pains of 7 yrs. duration; overlying skin red, later pruple, ulceration 6.5 cm wide, marked cachexia	local applications soot, lime water, etc., caused inflammation	?	gangrene in ulcerated area, entire tumor mass necrotic, surrounding tissue unaltered	pain ceased, entire tumor sloughed off gradually; base of tumor changed to simple wound; complete healing in 3–4 mos.; in perfect health, NED until sudden death from "adynamic fever" 4 yrs later, 11 yrs after onset.
5. Amard (prior to 1807) (68; 98)	F 43	ulcerated breast cancer	?	?	gangrene, necrosis, eschar formed, which sloughed extensively, leaving	promptly healed completely; end result unknown

					healthy ulcer no longer characteristic of cancer	
6. Garneri 1810 (2; 37; 68; 98)	F 50	extensive cancer, involving entire lt. breast, unbearable lancinating pains; ''travelled 10 leagues to physician''; putrid low-grade fever; complete pain relief for 2 wks. then worse than ever	?	?	inflammation, then gangrene, entirely destroyed neoplastic tissue by 25th day	pain ceased, ulcer cleaned up, complete healing by 56th day, ''returned home cured''; end result unknown
7. Boyer 1851 (4; 6; 68)	F adult	very extensive inoperable cancer lt. breast; weak, cachetic	?	?	gangrene involving entire neoplasm	necrotic gangrenous tumor sloughed off; very extensive wound healed completely; numerous recurrent nodules soon appeared in scar, progressed; death 8 mos. later
8. Dupuytren 1829 (20; 68; 98, case 54)	F 40	extensive scirrhus carcinoma; surgery refused; affected breast voluminous, crepitant to touch, as if air was circulating in it; fever, frequent emesis for 48 hrs.; almost moribund	?	3 incisions to evacuate necrotic tumor tissue chlorinated compresses; necrotic portions cut off	inflammation, gangrene in large portions of tumor and breast; blackened; swollen; no sepsis	necrotic pieces of tumor emerged from incisions, breast reduced ⅓; necrotic tissue detached themselves; 4 wks. after gangrene developed, NED, considered cured; not traced
9. Fristo 1831 (6; 36; 68; 98, case 53)	F 60	enormous ulcerated inoperable breast cancer, involving axillary lymph nodes; repulsive odor	calcium chloride solution applied	none	skin and tumor tissue in breast and axilla became gangrenous	ulcer healthier, soon covered by healthy granulations, growth flattened down, forming solid very extensive cicatrix in concentric rings, adherent to all neighboring tissues; NED, few mos. later; end result unknown
10. Jackson 1946 (68; 109)	F 70 to 80	scirrhus tumor breast of 40 yrs. duration, almost stony hard	none, due to age of patient	none	tumor ulcerated, sloughed away piecemeal until it was all discharged	wound healed, in perfect health; end result unknown

SERIES H:
BENEFICIAL EFFECTS OF LIGHTNING OR ELECTROPUNCTURE ON BREAST CANCER: 4 CASES

Since only one case of breast cancer affected by lightning was found, it is given in detail. Eason reported in 1776 as follows:

> "Some years ago one Mrs. Wynne of Abraken in y^{e} county of Meath, (Ireland) after delivery of a child, was affected with a hard scirrhus tumour on her left breast. For the removal of it she was put upon a course of medicine and proper regimen by Dr. Hicks. But as he found it to be very stubborn, and was afraid that it might prove cancerous, he desired her to go to Dublin to have y^{e} advice of some eminent surgeons. She went there and consulted Messrs. Daunt and Lister, who recommended to her to return to the country and pursue y^{e} same course of medicine for sometime longer; as they considered cutting off the breast, or extirpating the tumour, to be the last remedy.
>
> "Matters continued much in the same state as they had been for several months, when she accidentally received a blow from lightning, as she stood at the window observing a heavy thunder shower. The lightning by which she was struck set fire to y^{e} roof of the house which was of thatch; it forced y^{e} chimneypiece from y^{e} wall and raised y^{e} carpet from y^{e} floor.
>
> "Mrs. Wynne received y^{e} stroke on the left shoulder, from where it passed across y^{e} diseased breast and down her back. The colour of her silk gown was discharged in several places; y^{e} flannel on her breast was a little burnt, or rather it appeared as if an iron, not very hot, had been drawn across it. She fell to the floor and remained without the use of her limbs till night. But upon their being rubbed with flower of mustard spirits, she recovered y^{e} use of them. Two days after this accident, Dr. Hicks visited her and found to his great surprise that the tumour of her breast was much softer and considerably diminished. In a short time after, it entirely disappeared; although for a considerable space before it had resisted y^{e} power of every medicine which could be exhibited.
>
> "From this case a question in practice naturally occurs. Since lightning and electricity are of the same nature, should we not be encouraged to try y^{e} electric shock against indurated swelling glands? And may it not serve at least to assist other remedies, when the case is stubborn. . ."(22)

(Comment: It may be of interest to note that Allison reported a case of cancer of the lip and chin which disappeared after the patient was struck by lightning. (Lancet 1: 77. 1880.)

Apparently, not until 1897, did any physicians consider administering electric shock to breast cancers!

Reading, of Philadelphia, then reported his experiences with frequent and long continued "electropunctures" of cancers, (15–20 milliamperes for 10 minutes each). Three cases of advanced breast cancers were successfully treated by this method. The tumors became inflamed, followed by suppuration and there was complete recovery. These patients had all refused mastectomy. (83a)

However, in the last few years a number of surgeons and radiologists have become interested in hyperthermia alone or as an adjuvant to radiation or incomplete surgical removal for various types of accessible neoplasms, including breast cancers. Such therapy

can be administered by radiofrequency or microwave-induced (58a) heat applicators of various wave lengths. Each year since April 1975, there have been national or international meetings on hyperthermia and cancer, a subject which had been ignored for so long. (69)

Bier (3a) induced acute inflammation and fever in cancer patients by injecting whole blood from pigs in the region of the tumor subcutaneously. His only breast cancer patient presented on March 9, 1920 with a very large hard tumor of the chest wall with an ulcerated area 9.5 × 4 cm. in diameter. There was a supraclavicular metastasis 5 cm. in diameter, the sternum was protruding due to the tumor and there were numerous bluish-red skin metastases. On March 10, 1920 the patient was given a single injection of about 20 cc. of pig blood around and partly into the tumor. The next day an "intensive x-ray treatment" was given. Continuous fever and sweating occurred. By April 26th, 1920 all the tumors had disappeared and the ulcerated area showed "excellent scar formation." There appeared to be "excellent local healing." Fever and sweating continued. By the end of May or 11 weeks after the blood injection innumerable metastatic nodules began to appear in the skin: "cancer en cuirasse." However the treated areas remained almost free of cancer. The disease then progressed causing death on August 30, 1920. (3a)

Bier attributed his results in this and a few other cases as due to inducing acute inflammation in the tumor area. In conclusion he stated "I doubt that it will ever be possible to permanently improve or cure malignant tumors by this or similar procedures, but the changes described above justify further cautious trials." (3a)

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PART III

Immunotherapy, Effects of Bacterial Vaccines

PART III

Introduction

The mixed bacterial vaccine (MBV) developed by William B. Coley, M.D. in 1893 has been discussed in Part I, pp. 146–158. In Part III, we have assembled all the mammary cancer cases so treated. Until our studies of this method began in 1940, no one had realized that there were so many different preparations made of this vaccine, beginning in January 1893, of which three were far more potent than the rest, namely the Buxton VI, Tracy X and XI. We were the first to name these different formulae and to find out which ones were used in each case.(57;58) A brief description of the first 13 is given in Reference #57. Coley gave the detailed formulae for Tracy's X and XI in Reference #19.

These vaccines were prepared from either heat-killed (the majority) or filtered cultures of Streptococcus pyogenes and Serratia marcescens (originally known as Bacillus prodigiosus). The unfiltered types were more effective. MBV was called Coley's Mixed Toxins during his lifetime.

Because Coley concentrated upon treating sarcomas with his vaccine, relatively few breast cancer patients received MBV. Only 87 microscopically proven cases so treated were found, 60 of which were inoperable, or terminal, with metastases, when MBV was begun. Despite these factors complete regressions of the local or metastatic lesions occurred in 13 cases, marked or partial regression in another 15, marked pain relief (especially when due to bone metastases) in 14 cases, weight gain in six cases. Since the tremendous importance of duration of immunotherapy was not recognized until very recently, most of these inoperable cases received injections for less than two months. Of the nine inoperable patients who survived for five or more years, (the first four apparent cures); duration of injections ranged from five to 19 months. The frequency in these successful cases was daily or three times a week at first, gradually decreasing the frequency later on.

It is of interest that even among the far advanced cases which ultimately succumbed to the disease there was very marked immediate improvement, ascites and pleural effusion ceased, pain ceased and bone metastases regressed. In six patients who had had lymphedema (one for four years), the swelling of the arm decreased.

Of the 17 operable breast carcinoma cases of which we have been able to obtain detailed histories and follow up information, one developed metastases 12 years later, which caused death 14 years after onset. Eight remained free from disease when last traced, five to 43 years after onset. The other three patients were traced well less than five years after onset. The first treated by Packard may well have died subsequently. The other two were treated by Matagne in Belgium. They received injections into the tumor area, one prior to mastectomy, the other as the only treatment which caused complete regression of the scirrhus carcinoma. These two cases may well have been permanent cures, since this technique was more effective in increasing host resistance than postoperative injections. *None of these MBV treated cases developed lymphedema.* (See below, Series 1.)

In addition five patients with operable *sarcoma* of the breast received MBV after surgery. Three of these were recurrent and one had bilateral disease. All recovered and were traced free from further evidence of disease 6 to 67 years after onset. (See below, Series 2.)

In view of the excellent results in patients with operable breast carcinomas and sarcomas who received adjuvant bacterial MBV either before and/or after surgery—it would seem wise now to undertake cooperative trials here and abroad using this combination, and compare the results with those achieved with adjuvant radiation or chemotherapy. MBV is so well tolerated by the patients and causes none of the unpleasant side effects of these other modalities, which should be an added incentive to such a trial.

PART III, SERIES 1:
OPERABLE MAMMARY CARCINOMA TREATED BY COLEY MBV:
12 CASES

Physician Reference	Sex Age	Diagnosis Date of Onset	Treatment Other Than MBV	MBV Therapy	End Result
1. Packard (2; 4)	F 56	3 times recurrent carcinoma (onset August 1892)	3 operations 1894, 1895, 1896	May 1896: Coley MBV (Buxton VI) following 3rd operation; did not prevent further recurrences for which 2 more operations were performed	MBV continued at least until February 1897; end result unknown
2. Matagne (35, Case 4)	F 63	ulcerated extensive scirrhus carcinoma with axillary metastases (onset 1896)	mastectomy May 1902; 6 mos. later recurrent pea size nodule excised	preoperative Coley MBV (Buxton VI) for 1 month into tumor area April 1902 (febrile reactions 39°–40°C.)	NED alive and well 1905, 11 yrs. after onset
3. Matagne (35; 36, Case 14)	F adult	carcinoma size of man's fist with numerous axillary metastases	involved tissues then removed	preoperative Coley MBV into tumor area	NED alive and well 5 yrs. later
4. Matagne (35; 36, Case 18)	F 41	carcinoma lt. breast	tumor area fulgurated 1910	preoperative Coley MBV into tumor area	no recurrence or metastases; in good health 1953, 43 yrs. later
5. Matagne (35; 36, Case 17)	F 55	carcinoma size of hen's egg	mastectomy	preoperative Coley MBV into tumor area	NED 3 yrs. later
6. Matagne (36, Case 20)	F 65	scirrhus carcinoma (onset 1911)	untreated	Coley MBV caused complete regression	NED 18 mos. later; not traced subsequently
7. Matagne (36, Case 24)	F 39	carcinoma	growth removed prior to MBV	postoperative Coley MBV subcutaneously 1916 or later	NED reported as cured 1953
8. Calkins (2; 4)	F 40	bilateral carcinoma (onset 18 mos. after severe contusions in auto accident)	bilateral Halsted mastectomy 1917	postoperative Coley MBV (Tracy XI) begun 2 wks. later, every 48 hrs. for 4 mos., then twice a wk. for another 6 mos.	NED in good health then sudden death, coronary occlusion April 17, 1947, 30 yrs. after onset

PART III, SERIES I:
OPERABLE MAMMARY CARCINOMA TREATED BY COLEY MBV:
12 CASES

Physician Reference	Sex Age	Diagnosis Date of Onset	Treatment Other Than MBV	MBV Therapy	End Result
9. Calkins (2; 4)	F 46	recurrent carcinoma lt. breast (with axillary and cervical metastases)	radical mastectomy for growth size of lemon May 1916; considerable necrosis of skin, took 2 mos. to heal; at 2nd operation July 1917 scattered metastatic nodes in axilla, cervical region removed	Coley MBV (Tracy XI) begun immediately after 2nd operation, given every 48 hrs. for 6 mos. stopped for a month then twice a week for 4 more mos.	NED for 12 yrs. then metastases occurred causing death 14 yrs. after onset (no further toxins given)
10. W.B. Coley (2, 4, 23, 38)	F 31	rapidly growing carcinoma rt. breast (had had extensive giant cell tumor femur involving knee joint 10 yrs. before, recovered after incomplete curettage, Coley toxins)	1922 adenofibroma rt. breast, with extensive acute mastitis, excised 1923; another rapidly growing tumor in another area of breast removed October 1924 (carcinoma); x-ray (9)	Coley MBV (Parke Davis XIII) twice weekly November 1924 in gradually increasing doses i.m.	NED in good health until death coronary occlusion and cardiac failure May 15, 1943, 18½ yrs. after onset
11. Dodd (2)	F Adult	carcinoma with axillary metastases, lymphedema; 3 mos. after surgery, intolerable pain in spine, lower thorax lumbar region; patient hopeless, depressed	radical mastectomy 6 mos. after onset, August 15, 1936	Coley MBV (Parke Davis XIII) October 15, 1936 given into proximal swollen arm i.m. weekly for 12½ mos., reactions 101°–102°F.; back pain disappeared, also lymphedema of arm; by November 1937 in radiant health	NED last seen November 1948; 12½ yrs. after onset
12. Riggins (2; 38)	F 49	infiltrating intraductal carcinoma rt. breast, metastasis to 1 axillary node 1958; to supraclavicular node & rib, 1971; patient had pulmonary T.B. at 19, received pneumothorax every 3 wks. for 10–11 yrs. with fluoroscopies each time; onset August 1958	rt. radical mastectomy, August 1958; cobalt (7) after excision of metastases February 1971; 5 more to spine metastases March 1971, estrogen 1971–78; tamoxifen for further metastases	Coley MBV (Johnston XV) weekly i.m. in gluteal region and thighs. No febrile reactions. Given for about 1 yr. after mastectomy	January 1969 influenza; December 1969 fell, broke wrist; May 1970 metastases to rib developed; not diagnosed until January 1971 when pain occurred; excised with supraclavicular node 1/29/71; mugged February 1971; vertebral metastases then found, disease quiescent 1972–1981; then reactivated; controlled on tamoxifen; death metastases April 29, 1982, 23½ yrs. after onset

PART III, SERIES 2:
OPERABLE MAMMARY SARCOMA TREATED BY COLEY MBV: 5 CASES

Physician Reference	Sex Age	Diagnosis Date of Onset	Treatment Other Than MBV	MBV Therapy	End Result
1. W.B. Coley (2; 4)	F 22	4 times recurrent sarcoma rt. breast, considered hopeless	4 operations by Kammerer at Mt. Sinai Hospital; shortly after beginning MBV Coley removed 2 small recurrent masses from pectoral region; another attempt at removal October 1906	Coley MBV (Tracy X) July 1906; 3 mos. later another small local recurrence (had not developed as promptly as others); MBV continued at home by family physicians	complete recovery NED 1931, over 25 years after onset
2. Matagne (35, Case 13)	F 36	recurrent sarcoma lt. breast	primary removed surgically 1907; 2nd operation given after about a month of MBV injections	Coley MBV (Buxton VI) given for recurrence daily into tumor; febrile reactions 39°–40°C.	no further recurrence; alive and well 6 yrs. later
3. Haines (4)	F 26	round cell sarcoma rt. breast, metastasis in pectoral muscles	radical mastectomy June 1911	Coley MBV (Tracy XI) postoperatively for 1 yr.; gained 50 lbs.; "felt well and happy"	no recurrence; alive and well 1929, died about 1933, 22 yrs. after onset, cause of death unknown
4. Calkins (4)	F 61	small rounded cell sarcoma both breasts (onset shortly after severe bruising in carriage accident February 1913) bilateral axillary involvement	bilateral radical mastectomy (Halsted) June 12, 1913; x-ray (6) during MBV therapy	Coley MBV (Tracy XI) begun shortly after surgery, continued steadily for 4 mos., then twice weekly for monthly intervals with 2 wks. rest between each month	no recurrence, in good health 6 yrs., then developed diabetes which proved fatal
5. E.H. Ochsner (2, 4)	M 18	recurrent round cell sarcoma lt. breast causing drawing deep depressing pain; onset April 1915, 2 mos. after being hit in breast region by stone	growth removed by Percy July 1915; recurrence 2 yrs. later, excised December 1917 by Ochsner	Coley MBV (Parke Davis XIII) shortly after second operation, all i.m., mostly above lt. breast, several in lt. arm; mild reactions (to 100.4°F.) continued 15 months	no further recurrence, appendectomy 1925; prostatectomy 1980; in good health August 1983, at 86, 68 yrs. after onset

PART III, SERIES 3:
INOPERABLE OR TERMINAL MAMMARY CANCERS TREATED BY MBV FOR 3 MONTHS OR MORE: 27 CASES

Physician References	Sex Age	Diagnosis, Date of Onset	Treatment Other Then MBV	Mixed Bacterial Vaccines (MBV)	Immediate and Final Results
1. W.B. Coley (7, case 7)	F 43	inoperable carcinoma breast, supraclavicular metastases	untreated prior to toxins; mastectomy June 1894, 6 wks. after toxins begun	April 1894: filtered Coley MBV for 6 wks. prior to and 3½ mos. after surgery	*marked regression in 4 wks.*; at surgery *remains of growth had areas of fatty degeneration*; end result unknown
2. W.B. Coley (4; 12; 14, case 18; 18; 23, p. 134; 38)	F 35	twice recurrent inoperable carcinoma rt. breast, axillary metastases, lymphedema of 4 yrs. duration (onset 1890, after injury to breast)	February 1894 primary excised, immediate recurrence, mastectomy February 1895 by Coley with removal of most of involved axillary nodes; again recurred (2½ × 6½ cm.); January 1896, 3rd operation (incomplete and difficult)	spring 1895 Coley MBV (Buxton VI) 3 times a week (reactions to 102.6°F.); small doses had no effect, with larger doses disease controlled for a time, disease again quickly recurred after 3rd operation; by increasing dosage, frequency of injections, was soon controlled, complete healing, toxins continued over 1 yr., resumed for a short time fall 1897	*all induration disappeared except 1 area on rib, lymphedema improved; complete healing* by January 1897; *axillary growth no longer palpable; infiltrated pectoral muscles normal on palpation, 10 lb. wt. gain; well over a yr.*, when MBV stopped, recurrence, supraclavicular metastases of rapid growth; disease no longer controlled, involved liver, ascites; death December 1897, 7 yrs. after onset
3. W.B. Coley (4; 14; 23)	F 56	twice recurrent inoperable bilateral breast carcinoma (onset January 1894)	bilateral mastectomy; recurrence excised; 2nd recurrence untreated; localized skin lesions excised under cocaine, paracentesis several times for ascites, 1900–1905	October 1897 Coley MBV toxins (Buxton V, filtrates) daily for 4 wks. small doses; then 3 times weekly for 18 mos.; thereafter with intervals of rest for total of over 3 yrs.	*hard recurrent nodules disappeared in 4 wks., general condition much improved*; 4 or 5 sharply localized skin infiltrations developed during MBV therapy; May 1900 ascites; death 1905, 10 yrs. after onset
4. Bott & W.B. Coley (4; 21; 23; 38; 57)	F 39	inoperable carcinoma of both breasts, extensive supraclavicular and cervical metastases involving entire lt. cervical region, clavicle to mastoid, prognosis hopeless;	nodules in lt. breast removed November 1905 (cyst); May 1906 (carcinoma); a wk. later simple mastectomy (axilla not explored); 1 yr. later rt. breast	February 1909 Coley MBV (Tracy XI) begun by Bott, directly into cervical tumor and in pectoral region; using both filtered and unfiltered Tracy XI & XIF	*marked improvement in 4 wks., all evidence disease disappeared in 6 mos., complete recovery, gained 20 lbs., well, NED for 15 yrs.*; 1924 developed tumor in rt.

		had had polio at 6, resulting in severe scoliosis requiring brace which caused constant irritation to lt. breast (onset 1906 in lt. breast, early 1908 in rt. breast)	involved; simple mastectomy, February 1908; hard carcinomatous mass in entire lt. pectoral then developed; thyroid extract given; 1925 axillary lesion excised	and Parke Davis XII & XIIF (total 160 in 2 yrs.)	axilla, refused further treatment; disease progressed, widespread skeletal metastases, *death September 1925, 19½ yrs. after onset*
5. Lagueux (4; 23, p. 168; 57)	F 61	inoperable carcinoma lt. breast recurrent in rt. breast with axillary metastases; again recurred after 2nd mastectomy, motion of arms limited and painful, general condition very poor (onset 1906 or before)	lt. radical mastectomy 1906; recovery poor; rt. radical mastectomy 1907; pain persisted	April 21, 1907; Coley MBT (Tracy XI) daily for 5 mos (aggressive dosage)	*pain soon ceased; recurrent nodules regressed completely in 5 wks., appetite returned, gained weight and strength, in excellent health, NED December 1913, over 7 yrs. after onset*
6. Lagueux (4; 23, p. 168; 57)	F 50	inoperable carcinoma lt. breast, recurrent in cicatrix, limited motion of arm; also mass in rt. breast, nipple retracted, oozing foul discharge; general condition poor (onset 1904)	August 1908 mastectomy 4 yrs. after onset, recurrence untreated	May 29, 1909; Coley MBV (Tracy XI) daily for 3 wks. by Lagueux, thereafter by family physician, exact duration unknown	*all pain disappeared almost immediately, swelling lt. arm decreased; tumor in rt. breast decreased 50% in 1st month; complete recovery, NED 1912,* 8 yrs. after onset
7. W.B. Coley (2; 4)	F young adult	recurrent inoperable carcinoma rt. breast involving lt. breast, abdominal metastases, massive ascites (onset 1906 shortly after lactation of first child)	operated by Makins, London, 1906; recurrence incompletely removed, metastases untreated	September 1909 Coley MBV (Parke Davis XII for 2 mos., then Tracy XI) given by Umney in England, continued 10 mos.; resumed November 1910; small doses weekly (Parke Davis XII, then filtrate, XIIF, later Tracy XI); total duration 19 mos.	*at first improved,* then late February 1910 ascites slowly increased, lt. pleural effusion; under steady use of Tracy XI, *ascites and effusions decreased then disappeared by April 1910; resumed normal life;* ascites recurred January 1911, with abdominal metastases and numerous skin nodules but *under further MBV they softened and disappeared;* disease progressed rapidly after MBV was stopped; death May 28, 1911, 5 yrs. after onset

PART III, SERIES 3, INOPERABLE OR TERMINAL MAMMARY CANCERS TREATED BY MBV FOR 3 MONTHS OR MORE, (cont'd)

Physician References	Sex Age	Diagnosis, Date of Onset	Treatment Other Then MBV	Mixed Bacterial Vaccines (MBV)	Immediate and Final Results
8. Sherman (4)	F 45	inoperable recurrent carcinoma rt. breast, metastases to lt. breast & omentum; pain, vomiting, ascites; onset primary October 1913, onset omental metastases April 1915	mastectomy shortly after onset; local recurrence excised March 1914; lt. mastectomy for metastases October 1914, 2 other operations; December 1914 to March 1915 5 radium treatments caused burn (took 2 yrs. to heal); December 1915 to March 1916 ascites drained (4 gallons each time)	May 1915, Coley MBV (Tracy XI) daily, then every other day; by September 1916 only one a week; no injections October 1916 due to attack of grippe; resumed November 1916, weekly for 1 month; resumed February 12, 1917, daily, good reactions (100–102.8°F.)	*metastatic nodules disappeared, also mass in abdomen, pain & ascites ceased, appetite & color good;* duration all of 1916 she "held her own"; pain ascites returned somewhat for 6 wks, then again began to disappear; *regained lost weight;* December 1916 neuralgic pains in hips, appetite & color not so good; January 1917, ascites returned; February 1917 metastases on chest; end result unknown
9. W.B. Coley (2; 4; 38)	F 63	inoperable adenocarcinoma rt. breast, metastasis axilla, lt. breast and supraclavicular region, general carcinomatosis all skeletal bones (onset prior to 1926)	rt. radical mastectomy spring 1926; March 1933 x-ray (15) totalling 10,450 r. to skeletal lesions, causing marked radiation sickness, nausea, emesis	April 7, 1933 Coley MBV (Parke Davis XIII) small doses moderate reactions, continued twice weekly all summer; March 1934 toxins resumed for 5 mos.	during 1st weeks *superficial tumors disappeared, general health markedly improved, gained weight, strength, in 3½ mos. all nodules had disappeared, including mass on posterior lt. shoulder girdle; by February 1934 NED in breast, axillae or supraclavicular regions;* skeletal x-rays March 1934 showed *decided improvement some bones, others had progressed;* disease not controlled; abdominal metastases, death September 1934, about 9 yrs. after onset
10. Johnston (29; Case 4)	F 67	terminal adenocarcinoma breast, moribund, cachectic; ulcerated fungating mass eroding entire chest wall (2 yrs. duration)	untreated except for biopsy	Coley MBV (Johnston XV) 48 i.v. in 9 mos.	*sustained improvement; gained weight, lesion underwent necrosis with gradual sloughing;* during heat wave, sudden death from

					heat stroke (not receiving toxins when stricken), death three yrs. after onset
11. Johnston (29, II, Case 3)	F 46	adenocarcinoma breast, axillary and hepatic metastases, pleural effusion, 20 lb. weight loss, abnormal liver function tests (5 yrs. duration)	radical mastectomy; x-ray: 1st course 3200 r, 2nd 40 treatments; x-ray castration; repeated thoracentesis for effusion; thoracotomy for empyema; underwater drainage several mos.	Coley MBV (Johnston XV): 136 in 12 mos.	*liver function returned to normal; pleural effusion ceased;* after an accident thoracentesis done by another physician, resulting in empyema; did well for several mos. after empyema therapy, then pneumonia opposite side caused death, 1 yr. after beginning MBV, 6 yrs. after onset
12. Johnston (29, II, Case 4)	F 48	adenocarcinoma breast, osteolytic metastases to spine, pelvis, bedridden severe bone pain (4 yrs. duration)	radical mastectomy; x-ray; HN_2; radiation castration; testosterone; cortisone	Coley MBV (Johnston XV); 75 i.v. in 11 mos. (slight increase in pain noted during chills)	*bone pain ceased, able to walk in a month, filling of osteolytic lesions, improvement continued 11 mos.* then fulminating metastases developed
13. Johnston (29, II, Case 6)	F 56	adenocarcinoma breast, with pathologic fracture lt. knee and humerus, metastases to femora, pelvis, ilium and ischium; marked bone pain (2 yrs. duration)	radical mastectomy; x-ray (30) testosterone	Coley MBV (Johnston XV); 8 i.v. in 5⅔ mos.	*pain markedly decreased during MBV theapy;* then developed CVA, thought to be due to brain metastases, died shortly thereafter, 2½ yrs. after onset
14. Johnston (29; Case 7)	F 45	adenocarcinoma breast, pleural effusion, lt. Horner's syndrome, less vision lt. eye, paralysis lt. hand (5 yrs. duration)	radical mastectomy; x-ray (3200 r); testosterone; repeated thoracenteses	Coley MBV (Johnston XV); 230 i.v. in 15 mos.	*Horner's syndrome ceased; vision normal, no further thoracentesis required for 15 mos.;* after MBV was stopped pleural effusion rapidly recurred, also Horner's syndrome, death a wk. later, 6⅓ yrs. after onset; autopsy revealed pleural, lung and supraclavicular metastases
15. Johnston (29; Case 8)	F 50	adenocarcinoma breast, bilateral lung metastases supraclavicular nodes, osteolytic lesions, vertebrae, femur, ischium, ilium; severe bone pain marked anemia (2 yrs. duration)	radical mastectomy; x-ray (4 courses totalling 10,200 r)	Coley MBV (Johnston XV) 125 i.v. in 12 mos.	*bone pain decreased during MBV therapy but x-rays showed increasing lesions;* death 1 yr. after beginning toxins, 3 yrs. after onset

PART III, SERIES 3, INOPERABLE OR TERMINAL MAMMARY CANCERS TREATED BY MBV FOR 3 MONTHS OR MORE, (cont'd)

Physician References	Sex Age	Diagnosis, Date of Onset	Treatment Other Then MBV	Mixed Bacterial Vaccines (MBV)	Immediate and Final Results
16. Johnston (29; Case 11)	F 56	adenocarcinoma breast, bilateral cervical node, lung and cervical vertebrae metastases, marked dyspnea, bone pain (4 yrs. duration)	radical mastectomy; x-ray (3200 r); bilateral oophorectomy; testosterone	Coley MBV (Johnston XV) 224 i.v. in 18 mos.	slight increase in dyspnea during reactions; *marked decrease in cervical nodes, decreased bone pain continued during MBV therapy*, then fulminating metastases, death 18 mos. after beginning MBV, 5½ yrs. after onset
17. Johnston (29; Case 14)	F 39	adenocarcinoma breast, widespread osteolytic metastases, marked cachexia (4 yrs. duration)	radical mastectomy; x-ray: 6700 r to chest, 2000 r to rt. hip, 2000 r to back; x-ray sterilization, testosterone	Coley MBV (Johnston XV) 65 i.v. in 4½ mos., slight increase in pain during reactions	pathologic fracture proximal humerus; *decreased bone pain, 8 lb. weight gain; subjective improvement during MBV therapy*, then died rapidly advancing disease nearly 4½ yrs. after onset
18. Adelman (2)	M 55	large cell carcinoma rt. breast, axillary metastases (onset September 1953); severe osteoarthritis lumbar spine, knees, hips, April 1956; metastases lt. retina October 1956 causing retinal detachment, eventual blindness; surgery refused	radical mastectomy April 1954; postoperative x-ray May 1954; stilbesterol (15 mg. daily) begun August 1957, causing gynecomastia of lt. breast; cholecystectomy February 1959; stilbesterol continued (10 mg. weekly)	Coley MBV (Johnston XV) August 1957 subcutaneously at 4–6 wk. intervals, no reactions; 1960, acute allergic dermatosis rt. arm; toxins continued 1953–1963	*lesion in rt. eye disappeared, vision good*; February 1965 metastases to brain, lung, liver; "*course amazingly free of any real discomfort; weakness predominant finding*"; death October 16, 1965, 14 yrs. after onset
19. Riggins (2)	F 38	recurrent metastatic carcinoma lt. breast; (onset Fall 1962 after 12 yrs. of psychic trauma—marital)	simple mastectomy, Fall 1962, 1 wk. after discovery of lesion; recurrence in scar, Fall 1963; cobalt and chemotherapy that Fall; further chemotherapy 1976–1978 for metastases to pelvis, spine and ribs (cytoxan, methotrexate, 5 FU)	December 1963: Coley MBV (Tendler XVI) concurrent with cytoxan; resumed March 1971 for metastases	*metastases regressed, remained in fine health*; divorce 1965; remarried 1970; early 1971 severe psychic trauma (relative dying pancreatic cancer); metastases, March 1971; *disease again regressed*; well until 1976, then metastases to pelvis; died 1979, 17 yrs. after onset

20. Cole (2)	F 36	bilateral adenocarcinoma, primary in lt. breast; osteoblastic and osteolytic metastases cervical spine, entire dorsal spine, pelvic bones, proximal femora, lower ribs; anorexia, 30 lb. weight loss; anemic	lt. radical mastectomy Aug. 1966, rt. simple mastectomy Feb. 1967; Laetrille for 4 mos. that spring; gained some weight but developed back pain (thoracic); which increased despite iron, calcium, testosterone, Laetrille	MBV (Tendler XVI) begun Aug. 27, 1967: 15 i.v. in about 3 wks., then maintenance therapy (1 i.d. a week for over 3¼ yrs.)	*excellent response; did well to Dec. 1970*, then rapid downhill course, death Dec. 14, 1970, over 4½ yrs. after onset
21. Cole (2)	F 69	inoperable adenocarcinoma breast	mastectomy 1960, 5 FU also given	November 10, 1967: MBV (Tendler XVI)	*alive and well August 1968*; not traced
22. Rank (2)	F 73	breast carcinoma, metastases to nodes, skin, lung	radical mastectomy March 1966; radiation, stilbestrol, androgen 1968; 1969 estrogen, cortisone	June 1969: MBV (Tendler XVI, at first lot #122, later #134) i.d. and i.v. several mos.	*good response, skin lesions and nodes to lot #122 for 3 mos., no response to lot #134*; died December 1969
23. Rank (2)	F 38	carcinoma lt. breast, parasternal recurrence, incapacitating bone pain, highly suggestive of metastasis	lt. radical mastectomy for stage 1 lesion 1966; interstitial radiation for recurrence 1968	August 1969 MBV (Tendler XVI, #134) i.d. and subcut. given continuously for 18 mos.	*bone pain ceased; NED remained in good health*, NED until death from stroke 1979, over 13 years after onset
24. Rank (2)	F 70	breast carcinoma with metastases to nodes, lungs, bones, pleura	radical mastectomy 1965; estrogen, androgen	September 1969: MBV (Tendler XVI, lot #134) i.d. for 2 mos., then Sylvana XVII for 5 more mos.	*brief stabilization disease for 3 mos.*, then relentless progression, death April 1970
25. Rank (2)	F 59	advanced breast carcinoma, metastases to lt. upper and lower lung	radical mastectomy October 1966 (17 or 18 nodes involved), then radiation causing wound slough requiring skin grafting; stilbestrol during toxins continued to May 1971	February 1970: MBV (Tendler XVI) i.d. and subcut. for 6 mos.	*lung metastases regressed*, alive and well, N.E.D. April 1982, 16 yrs. after onset
26. Rank (2)	F 52	rapidly advancing metastatic breast carcinoma, liver extended below umbilicus, lt. cervical nodes involved; pleural effusion	rt. radical mastectomy elsewhere; then radiation, biopsy lt. cervical nodes; 5 FU; cytoxan; disease rapidly progressed	September 1970 MBV (Sylvana XVII) given intrapleurally for 3 wks. with 5 FU, MBV later resumed	*complete disappearance cervical nodes and hepatomegaly; liver and neck almost normal in 2 mos., pleural effusion subsided by December 1970*; disease progressed in mid-1971, causing death about a year later
27. Rank (2)	F 52	breast carcinoma with 10 positive nodes including apex and hilar; parenchymal lung metastases	May 1969: radical mastectomy, then radiation; cytoxan and 5 FU given during MBV	January 1971: MBV (Sylvana XVII) subcutaneously for 5 mos.	*in remission May 1971*, eventually died of disease

PART III, SERIES 3, SELECTED DETAILED HISTORIES (PROLONGED TREATMENT)

CASE 4: Carcinoma of both breasts, recurrent and inoperable, following bilateral mastectomy, with extensive metastases in the supraclavicular and cervical lymph nodes confirmed by microscopic examination by Dr. James Ewing of Memorial Hospital, New York.

PREVIOUS HISTORY: E.D., female, age 39, of Palmyra, New York. The patient's paternal aunt died of cancer of the breast at the age of 84, and several other members of the family had cancer. The patient had had a bad fall when five years old. At six, she developed poliomyelitis, resulting in a severe scoliosis of the spine, requiring a brace and corsets ever since her 15th year. Her left breast had received constant pressure and irritation from the aluminum corset worn prior to onset. The curvature caused a marked deformity of the chest, one lung being compressed into a very small space. Onset, early in 1905, a small swelling the size of a pea was first noticed in the left breast at the site of the irritation. There was occasional slight discharge from the nipple. For a year prior to operation there was pain of a sharp stinging character. The nodule was not attached to the deeper parts and the skin was freely movable. The patient was referred to Dr. William B. Coley on November 22, 1905.

SURGERY: This nodule was excised and diagnosed as a cyst, with no evidence of malignancy. A year later another small nodule appeared in the same vicinity and was also removed by Coley, requiring a more extensive operation under ether on May 16, 1907. Clinically this tumor seemed the same as the first, but microscopically there was a small portion in which carcinomatous degeneration had taken place. A week later the entire breast was removed. The axilla was not explored as the patient's condition did not permit prolonging the anesthesia. A year later another nodule appeared in the proximal *right* breast. It was exceedingly small when first detected, being hardly larger than a buckshot. It seemed slightly harder than those in the other breast and the skin showed the faintest evidence of adherence. Therefore, in February 1908 the entire right breast was amputated by Coley without exploring the axilla.

CLINICAL COURSE: In December 1908 the patient again consulted Coley because of involvement in the left cervical region. He found a well-marked recurrence in the pectoral region. The condition was clearly inoperable. As an experiment Coley tried Beebe's thyroid extract for a few weeks, but the tumors continued to increase in size and when Coley examined her in February 1909 there was a hard carcinomatous mass occupying the entire left pectoral region with involvement of the lymph nodes from the clavicle nearly to the mastoid. Coley gave the family an absolutely fatal prognosis, stating that he did not believe the patient could live more than six months. He was asked if it would be any use to try his mixed bacterial vaccine in such a case, and he replied that nothing could be gained other than possible a slight retardation of the growth, and that there was no hope of cure. In spite of this advice, the sister was very anxious that the treatment be tried, as she did not want the patient to feel that nothing was being done. By this time her weight had decreased to 80 pounds, with beginning cachexia.

MBV THERAPY (TRACY XIF, TRACY XIIF AND PARKE-DAVIS XII): In order to lessen the discomfort associated with the local irritation of the unfiltered Tracy preparation (XI),

Coley asked Dr. W. J. Bott of Palmyra, New York, who administered the MBV in this case, to use the filtrate (Tracy XIF), which he considered to be half the strength of the unfiltered and very much less irritating. The patient proved to be exceedingly susceptible. The initial dose was 0.5 minim, which was gradually increased to 3 minims. *The injections were made into the cervical tumor or in the pectoral region on either side.* Very small doses were sufficient to produce moderately severe reactions. Within four weeks Bott wrote Coley that marked improvement had occurred, and that the tumors were steadily decreasing in size. At this time the more potent unfiltered product was given (Tracy XI). Improvement continued steadily, and in August 1909 Bott wrote that the pectoral, axillary and cervical tumors had practically disappeared. At this time a bottle of the commercial preparation was used (Parke-Davis XII), and in September 1909 Tracy's unfiltered product (XI) was again administered.

Coley examined the patient on February 24, 1910 and could find no trace of the tumors in either the pectoral, axillary or cervical regions. The patient regained her normal health and stated that she had never felt better. There were no nodes palpable in the axilla and no lymphedema. During the first year of treatment she received 104 injections in doses of 0.5 to 3 minims. Although the patient objected to continuing the treatment, Coley persuaded her to do so, and injections were therefore continued with intervals of rest for two years until February 1911 during which time 160 injections were given. In April 1910, Tracy's filtrate was again given (XIF) and in October 1910, the Parke-Davis filtrate (XIIF).

CLINICAL COURSE: This case was first reported before the American Cancer Research Society in April 1911 by Coley. He examined the patient again in June 1911, and found her in perfect health with no trace of tumors in the cervical, pectoral or axillary regions. She was presented before the New York Surgical Society on March 13, 1912. At this time she weighed 100 pounds, her maximum normal weight, and a gain of 20 pounds since the beginning of MBV therapy.

She remained well and free from disease until March 1924, 15 years after the injections were begun. At this time a tumor developed in the anterior margin of the right axilla. Apparently no physician was consulted for a year, until March 1925 when she was examined by Dr. Walter A. Calihan of Rochester, New York. At this time the tumor was about 3 cm. in diameter, spherical in form and hard. There was definite attachment of the skin with dimpling in the center. Calihan stated: "The question of metastasis arising 18 years after onset is of great interest. . . . I am rather of the opinion that this is probably a malignancy developing in aberrant breast tissue. . . ." (i.e. not a late metastasis).

SURGERY: This tumor was removed surgically and a specimen sent to Coley. Ewing examined it and pronounced it a highly malignant carcinoma.

CLINICAL COURSE: The patient refused further treatment at this time. The disease progressed causing death 18 months later in September 1926 from general carcinomatosis of all the skeletal bones. This was 20 years after onset of her first carcinoma and 17 years after immunotherapy was begun.

REFERENCES: 4; 21; 23; 38; 57

COMMENT: In reporting this case in 1912, Coley cited Lagueux's two published cases of carcinoma of the breast well three and five years, stating that these were of particular interest for the reason that, as far as he knew from his own experience and from a careful review of the literature, "they were the only cases in which an inoperable recurrent carcinoma with glandular metastases, and with the clinical and microscopic diagnosis

unquestioned, that had ever disappeared under any method of treatment, and where the patient had remained well for a period of three years . . ."

Coley stated that although during his early experiments with the living streptococcus cultures he had tried the effect of inoculation upon carcinoma as well as sarcoma, after substituting the mixed vaccines of erysipelas and Bacillus prodigiosus he had practically limited the method to cases of inoperable sarcoma, believing it wiser to first establish its value in one class of case. Among his earlier cases, however, there was one of inoperable carcinoma of the floor of the mouth, involving the lower jaw, where the diagnosis was confirmed by microscopic examinations, in which the disease entirely disappeared and the patient was well at the last observation six years later.

He believed that these cases justified a further and more thorough systematic study of the vaccine in cases of carcinoma, especially since his earlier experiments were carried on with preparations much inferior to that available in 1912 (Tracy XI). He further believed that, taken together with the two cases of Lagueux, these furnished sufficient grounds for advocating the routine adoption of a systematic course of treatment with the MBV after all primary operations for carcinoma. This plan had already been adopted by a number of leading surgeons. The treatment could easily be carried out by the family physician and did not necessitate any interference with the daily occupation or routine of life of the patient.

He added that he did not think sufficient recognition had been given to the clinical observations of concurrent erysipelas infections in inoperable malignant tumors of all types, including carcinoma.* Finally Coley stated that these observations still further justified the conclusion which he had offered: having established, as he believed, the value of his treatment in sarcoma, and having been further influenced by the very striking result in the above case (E.D.), he believed it advisable to make further and more systematic studies of the effects of the MBV upon carcinoma (2;4). A few years later he added the following note: "Pressure of work and the rapidly increasing interest in the treatment of carcinoma by x-rays and radium have prevented our carrying out (this plan) . . . However, I have continued the use of the vaccine wherever possible as a prophylactic after primary operations for carcinoma, as well as a certain limited number of inoperable cases.

"The striking end-results in some of the older cases have again aroused a keen interest in the toxin treatment of carcinoma, and have proved most conclusively the value of the method."(4)

Korteweg (1910) called attention to Potherat's case of very late recurrence, reported before the Société de Chirurgie on October 20, 1909: This patient had had both breasts removed, one shortly after the other, by Potherat. She remained cured for 23 years when a recurrence (?) developed in the skin a short distance from the cicatrix. At this meeting he presented a specimen of the skin covered with multiple hard carcinomatous nodules, which had been removed from the sternal and epigastric region of this patient. The question is, are such cases recurrences, or a new development of cancer in an individual predisposed to the disease? He noted that cases of "recurrences" had been reported as occurring after 30 years by Lebhardt, 1902, and Bircher, 1907.(32)

CASE 8: Inoperable adenocarcinoma of the right breast, with metastases in the right axilla, recurrent five years later

*Note: In the last 42 years we have assembled 449 cases of malignant disease in which an acute infection or inflammation developed either spontaneously or by inoculation, causing marked benefit or complete regression in the majority. Of these, over 80 per cent had some form of pyogenic infection, principally streptococcal (erysipelas) or staphylococcal.(50) (For further references, see 21; 23; 38; 57.)

in the cicatrix, with metastases in the left supraclavicular region and left breast, as well as general carcinomatosis of practically all the skeletal bones, innumerable lesions in the skull, some in the spine, ribs and pelvis, many on the long bones, especially the femur.

PREVIOUS HISTORY: Mrs. E.K.McC., female, age 63, of Charleston, West Virginia. The family and previous personal history were not recorded.

SURGERY: The patient had a radical mastectomy of the right breast five years previously in the spring of 1926. The neoplasm was of long-standing at that time and there were metastases in the right axilla. The prognosis at that time was very grave.

CLINICAL COURSE: Immediate recurrence was expected, but the patient's general condition remained remarkably good. In late February 1933 she consulted Dr. William R. Laird of Montgomery, West Virginia. He found two or three little nodules about the scar, and a small mass in the left breast. The lungs were clear but there were extensive skeletal metastases. The patient was referred to Dr. William B. Coley on March 16, 1933. At this time the condition was so far advanced that Coley doubted the wisdom of attempting anything in the way of treatment.

RADIATION: A consultation was held with Duffy, the radiotherapist at Memorial Hospital and it was decided to radiate all the bones and then start MBV. Accordingly, from March 17th to April 6, 1933, 15 x-ray treatments were given totalling 10,450 r.

MBV THERAPY (PARKE-DAVIS XIII): The injections were begun by Coley about April 7, 1933, and were given in small doses, sufficient to produce moderate reactions. For a week after her return home there was marked "radiation sickness", nausea and vomiting, and muscular asthenia, but in spite of this fact Laird resumed the injections and the nausea and vomiting soon ceased. The patient gained considerable weight and strength. The superficial tumors in the left pectoral and supraclavicular region entirely disappeared after a few weeks, and there was marked improvement in the general condition. On June 27, 1933 Laird wrote that 4 minims of MBV caused a reaction of 100.6°F, but that this caused absolutely no discomfort and there was no loss of appetite. During the entire summer two injections a week were given, and by July 27, 1933 all the nodules had disappeared, including the mass in the posterior aspect of the left shoulder girdle. By September 22, 1933 Laird wrote: "I have never seen such a remarkable change in a patient's general condition. She is quite happy and insists that she is cured." On October 3, 1933 Laird wrote in regard to reducing the frequency to one injection a week and added that the patient did not object in the least to the treatment.

CLINICAL COURSE: In February 1934 the patient was again seen by Coley, who found her general condition remarkably good, and the weight normal. Careful physical and examination failed to reveal any evidence of recurrence in the left breast, axillary region or supraclavicular region, i.e., there was no external evidence of disease. The patient refused to have x-ray pictures taken at this time, saying she was on a holiday and would have the pictures taken at home. This was done two weeks later and the films sent to Coley and Duffy. In comparison with those taken a year before, it was noted that in some regions the lesions were somewhat more marked than before and in other regions the bones showed decided improvement. The patient was urged to have further radiation, but absolutely refused.

SECOND COURSE OF MBV THERAPY: Injections were resumed by Laird in Febraury 1934, and continued until about July 1, 1934. No details are available as to site, dosage,

frequency of injections or the type of reaction elicited during this course.

CLINICAL COURSE: The condition gradually became worse, metastases developed in the right upper quadrant of the abdomen with signs of obstruction. Death occurred in August 1934, over nine years after onset.

COMMENT: This case indicates the urgent need of continuing the injections in larger doses and with more marked reactions for some time after all clinical evidence of disease has disappeared, in order to achieve a permanent result, as was done in Case 4 (E.D.). It appears also to be advisable to begin MBV before administering radiation in such cases.

REFERENCES: 2; 4; 38

PART III, SERIES 4:
INOPERABLE OR TERMINAL MAMMARY CARCINOMA TREATED BY COLEY MBV FOR LESS THAN THREE MONTHS:
36 CASES

Physician References	Sex Age	Diagnosis, Date of Onset	Treatment Other Than MBV	MBV Therapy	Immediate and End Results
1. W.B. Coley (2; 38)	F 60	inoperable carcinoma rt. breast (6½ cm.); onset November 1892; also had severe organic heart lesion	no operation (heart condition); caustic potash; Bouchard's paste applied, biopsy, also flax seed poultices for very severe breast pain	November 20, 1893: filtered erysipelas toxins (4 doses 20–30 minims); filtered MBV (Coley type IV) 10 doses in tumor area causing sloughing, regression; toxins resumed for recurrence every 48 hrs. for 9 wks.	*growth disappeared in 2 mos.*, recurred 2 mos. later, with axillary metastases, disease not controlled, death carcinoma of breast and severe melancholia, December 13, 1894, over 2 yrs. after onset
2. W.B. Coley (9; Case III)	F 50	very extensive spherical tumor 56 cm. in circumference firmly fixed to chest wall, skin adherent, ulcerated below nipple, metastases to pleura, pericardium, suprarenal capsules (autopsy)	untreated	February 1895; Coley MBV (Buxton VII, filtrate) 1–20 minims for several wks., no reactions, overlying skin less tense, growth smaller, more movable; then Buxton VI (unfiltered), 2½–5 m., reactions 104°–105°F)	*tumor shrank steadily, ulceration deepened, masses necrotic tumor sloughed out, regressed over 50% in 8 wks.*; erosion of large blood vessel, uncontrollable hemorrhage, death
3. Howland (12)	F 62	inoperable scirrhus carcinoma lt. breast 6½ × 11½ cm.; adherent to chest wall, infiltrating skin, axillary metastases; (onset September 1894)	untreated except for biopsy; tumor became operable and surgery was advised but refused	February 1895: Coley MBV (Buxton VI) for 11 wks., injections resumed briefly July 1895	*tumor became movable on chest wall, regressed to ⅓ its former size in 13 days; pain ceased, axillary nodes decreased;* growth increased in size in 2 mos. after MBV was stopped; little effect when resumed; disease progressed, death February 22, 1897, 2½ yrs. after onset
4. Beale (4)	F 67	recurrent inoperable bilateral scirrhus carcinoma of rapid growth with metastases to lt. cervical lymph nodes, edema of lt. hand & wrist (primary in lt.	radical lt. mastectomy, 1895; rt. breast & cervical lesions untreated prior to MBV; metastases excised May 5, 1896 *no evidence of cancer remained*	mid-March 1896: Coley MBV (Lister Institute VIII) every other day for about 6 wks., 0.7 to 6 minims; no febrile reactions	*marked steady improvement in 2 wks.; in 6 wks. general health good, ate and slept well; lesion in rt. breast disappeared, cervical nodes regressed 75%, pain*

PART III, SERIES 4:, INOPERABLE OR TERMINAL MAMMARY CARCINOMA TREATED BY COLEY MBV FOR LESS THAN THREE MONTHS, (cont'd)

Physician References	Sex Age	Diagnosis, Date of Onset	Treatment Other Than MBV	MBV Therapy	Immediate and End Results
		breast) rt. breast lesion 4 cm. in diameter, hard, painful; cachexia			*ceased, edema of hand & wrist almost gone;* end result unknown
5. Wild (67)	F 66	inoperable scirrhus carcinoma lt. breast of 9 mos. duration, with axillary and supraclavicular metastases (autopsy)	untreated	January 1899 Coley MBV (Lister Institute VIII): 13 in 14 days totalling 83½ minims, no local reaction until 11th injection, then severe pain in breast; after 11 days final dose of 5 m. caused another marked local reaction (no fever or chills)	*gained a little weight* during treatment; when injections ceased disease progressed rapidly; death 3 mos. later
6. Wild (67)	F 50	twice recurrent scirrhus carcinoma lt. breast of 3 yrs. duration	mastectomy 1 yr. after onset; 2nd operation for local recurrence 15 mos. later; again recurred in 9 mos.	January 30, 1899 Coley MBV (Lister Institute VIII) daily i.m. for 24 days (total 210.5 minims); no febrile reactions	*no effect*, death 1 mo. after last dose
7. W.B. Coley (2; 4)	F 28	recurrent carcinoma rt. breast, metastasis to cervical, axillary and pectoral regions, losing weight; (onset 1901, 4 yrs. after local trauma)	2 nodules excised elsewhere 6 mos. after onset; local recurrence excised by Coley 1910, metastases untreated	February 1911 Coley MBV (Tracy XI) 14 given, reactions to 104°F	*right cervical mass almost disappeared in 9 wks., axillary, pectoral involvement became very movable*; end result unknown
8. W.B. Coley (2; 4; 38)	F 27	inoperable carcinoma rt. breast, clavicular metastases involving brachial plexus (onset, January 1923) arm, wrist drop, enormous lymphedema, paralysis	May 1923, egg size mass removed, then mastectomy by Sullivan; several courses x-ray 1923, another September 1926 for pain, 9 more September 1927	December 1927 Coley MBV (Parke-Davis XIII) i.m. daily for 5 wks. in small doses, then i.v.	*in 21 days could move arm for first time in mos., arm became normal, general condition much improved*; disease then progressed, quadriplegia, death June 1928, 5½ yrs. after onset
9. Johnston (29; Case 1)	F 64	inoperable adenocarcinoma breast with diffuse skeletal metastases (1 yr. duration)	radical mastectomy, x-ray (30)	Coley MBV (Johnston XV) 14 i.v. in 3 wks. caused severe muscle and abdominal cramps	*no apparent benefit*, refused further treatment, death 6 mos. later, 18 mos. after onset

10. Johnston (29; Case 2)	F 47	inoperable adenocarcinoma breast, extensive skeletal metastases, severe pain (3 yrs. duration)	radical mastectomy x-ray (45)	Coley MBV (Johnston XV) 17 i.v. in 25 days	*slight decrease in pain*, death 1 month after last injection, over 3 yrs. after onset
11. Johnston (29; Case 3)	F 38	adenocarcinoma breast with metastases to lungs, spine, hips, knees, severe pain (4 yrs. duration)	radical mastectomy; x-ray (3200 r)	Coley MBV (Johnson XV) 21 i.v. in 5 wks., increased pain in tumor sites during first 3 injections	*bone pain ceased for 2 mos.*, although x-rays showed increase in number and size of osteolytic lesions; died 5 wks. after last injection, over 4 yrs. after onset
12. Johnston (29; Case 1)	F 67	adenocarcinoma breast, multiple osteolytic metastases, severe pain (6 yrs. duration)	radical mastectomy; x-ray (3600 r); testosterone	Coley MBV (Johnston XV); 15 i.v. in 3 wks.	*bone pain decreased*, x-rays unchanged; *subjective improvement for 2 mos.*, then death, over 6 yrs. after onset
13. Johnston (29; Case 2)	F 43	adenocarcinoma breasts, diffuse abdominal, pelvic metastases, severe pain (8 yrs. duration)	bilateral radical mastectomy; x-ray (48); bilateral oophorectomy	Coley MBV (Johnston XV); 31 i.v. in 8 wks.	*no apparent benefit*, death 2 mos. after 1st MBV injection, over 8 yrs after onset
14. Johnston (29; Case 6)	F 61	adenocarcinoma breast, bilateral pulmonary, axillary metastases; 40 lb. weight loss; anorexia, depressed; (1 yr. duration)	simple mastectomy; 1 dose diethylstilbestrol	Coley MBV (Johnston XV); 45 i.v. in 2 mos.; refused further therapy	*pain decreased, less anorexic and mentally depressed, gained 10 lbs.*, died 2 days after last injection, 14 mos. after onset
15. Johnston (29; Case 9)	F 60	adenocarcinoma breast, bone metastases, severe pain (2 yrs. duration)	radical mastectomy; x-ray (30)	Coley MBV (Johnston XV) 36 i.v., 3 i.m. in 2 mos.	*decreased bone pain, 10 lb. wt. gain*, lost to follow-up
16. Johnston (29; Case 10)	F 63	adenocarcinoma breast, axillary, skeletal, liver and lung metastases, bone pain, severe cough, hepatomegaly	simple mastectomy: x-ray (46)	Coley MBV (Johnston XV) 46 i.v. in 3 mos.	*no apparent change* during MBV therapy; lost to follow-up thereafter
17. Johnston (29; Case 12)	F 56	large ulcerating adenocarcinoma entire breast fixed to overlying skin; axillary metastases (9 mos. duration)	simple mastectomy	Coley MBV (Johnston XV) 24 i.v. in 6 wks.	*no improvement*; lost to follow-up

PART III, SERIES 4:, INOPERABLE OR TERMINAL MAMMARY CARCINOMA TREATED BY COLEY MBV FOR LESS THAN THREE MONTHS, (cont'd)

Physician References	Sex Age	Diagnosis, Date of Onset	Treatment Other Than MBV	MBV Therapy	Immediate and End Results
18. Johnston (29; Case 13)	F 57	adenocarcinoma breast, metastases to skin over back, axillary nodes, bilateral pleural effusion (5 yrs. duration)	radical mastectomy: x-ray (3200 r); Au^{198}	Coley MBV (Johnston XV) 31 i.v. in 8 wks.; increased dyspnea, cyanosis during reactions	*no improvement*; rapidly advancing disease, death 2 mos. after beginning MBV, over 5 yrs. after onset
19. Cole (2)	F 73	inoperable adenocarcinoma breast (6 yrs. duration)	1959: radical mastectomy; 6 mercaptopurine	MBV (Tendler XVI) 14 intradermal in 3 wks. spring 1965	*no apparent benefit* death over 6 yrs. after onset
20. Cole (2)	F 61	inoperable adenocarcinoma breast (over 3 yrs. duration)	1962: radical mastectomy; Leukeran	MBV (Tendler XVI) 15 i.d. in 18 days ending April 20, 1965	*no apparent benefit*; death May 20, 1965, over 3 yrs. after onset
21. Cole (2)	F 61 (M.C.)	inoperable adenocarcinoma breast (duration over 4 yrs.)	April 1961 radical mastectomy; x-ray	MBV (Tendler XVI) 10 i.d. in 21 days begun May 20, 1965	*no apparent effect*, considered a failure, not traced
22. Cole (2)	F	inoperable ductal carcinoma breast	x-ray May 1964; radical mastectomy April 1965; 5 FU	MBV (Tendler XVI) 15 i.v. in 4 wks. ending Jan. 10, 1966	*objective and subjective improvement*; alive when reported few mos. later
23. Cole (2)	F 78	inoperable adenocarcinoma breast	mastectomy 1961	MBV (Tendler XVI) 15 i.v. in 27 days ending Jan. 6, 1966	*subjective improvement, did well for several mos.*; expired Jan. 1967 over 6 yrs. after onset
24. Cole (2)	F 40	inoperable adenocarcinoma breast	radical mastectomy December 1966	MBV (Tendler XVI) 15 i.v. in 21 days ending Jan. 23, 1967	*subjective improvement*; expired
25. Cole (2)	F 54	inoperable adenocarcinoma breast	radical mastectomy 1962; cobalt 1962	MBV (Tendler XVI) 12 i.v. in 8 wks. ending March 26, 1967	*no apparent benefit*; expired April 1968
26. Cole (2)	F 42	inoperable adenocarcinoma breast and ovary	mastectomy 1961; radiation 1966	October 2, 1967: MBV (Tendler XVI) 15 i.v. in 21 days	*no apparent benefit*; expired December 15, 1967
27. Cole (2)	F 54	inoperable adenocarcinoma breast	mastectomy 1964; cobalt April 1967	August 3, 1967 MBV (Tendler XVI): 11 i.d. in 13 days	*objective and subjective improvement; alive and well August 1968;* not traced

28. Cole (2)	F 56	inoperable adenocarcinoma breast	mastectomy 1962; oophorectomy 1964; 5 FU (maintenance)	April 20, 1967 MBV (Tendler XVI) 15 i.d. in 34 days	*objective and subjective improvement; alive and well August 1968;* not traced
29. Cole (2)	F 42	inoperable adenocarcinoma breast	mastectomy 1965; oophorectomy October 1965; radiation March 1967; 5 FU (maintenance)	March 16, 1967: MBV (Tendler XVI) 11 i.v. in 35 days	*subjective improvement temporarily;* expired August 29, 1967
30. Cole (2)	F 43	inoperable adenocarcinoma breast	mastectomy 1962; oophorectomy 1964; radiation 1966; Rand vaccine January and February 1967; 5 FU	July 14, 1967: MBV (Tendler XVI) 15 i.v. in 33 days, then maintenance therapy	*objective and subjective improvement; alive and well August 1968;* not traced
31. Cole (2)	F 57	inoperable adenocarcinoma breast	mastectomy August 1965; 5 FU	March 8, 1968: MBV (Tendler XVI) 18 i.v. in 10 wks.	*subjective response;* expired within 6 mos.
32. Cole (2)	F 45	inoperable adenocarcinoma breast	mastectomy; radiation, 5 FU	June 3, 1968: MBV 11 injections in 16 days	*no apparent benefit;* died
33. Cole (2)	F 45	inoperable adenocarcinoma breast	mastectomy; oophorectomy; 5 FU	July 8, 1968: MBV 12 i.v. in 16 days	*no apparent benefit;* died
34. Rank (2)	F 50	generalized metastases, breast carcinoma	June 1968 radical mastectomy for Stage 1; oophorectomy	March 1969: Coley MBV (Tendler XVI) i.v. for 2 mos.	*no apparent benefit;* died April 1969
35. Rank (2)	F 60	breast carcinoma with metastases to lymph nodes, lung and brain	radical mastectomy January 1969, then radiation; cerebral radiation and craniotomy for cerebral metastases, also cytoxan and cortisone	August 1970: MBV (Sylvana XVII) subcut. and intrapleural for 2 mos.	*some transient subjective improvement,* died
36. Rank (2)	F 70	inoperable inflammatory carcinoma breast	radiation, estrogen, androgen, thioTEPA	September 1969: MBV (Tendler XVI) i.v. for 2 mos.	*only response necrosis of skin tumor;* death November 1969

PART III, SERIES 5:
INOPERABLE MAMMARY SARCOMA TREATED BY COLEY MBV:
7 Cases

Physician, References	Sex Age	Diagnosis, Date of Onset	Treatment other than MBV	MBV Therapy	Immediate and End Results
1. Schmittle (63)	F 50	ulcerated, inoperable 3 times recurrent spindle cell sarcoma lt. breast, extending over greater portion lt. thoracic wall, into axilla & arm, under & over clavicle; arm very edematous, bound down to side, immovable; general condition very deteriorated; anemic; onset early 1890	large, foul smelling growth removed; 4 yrs. later recurrence removed	July 12, 1895: Coley MBV (Type IV, filtered) deeply into recurrent growth, each into a different area, 11 in 6 wks.; severe chills, reactions 103°–104°F. unless antipyretics were given; treatment then discontinued due to patient's weak condition	*some improvement evident after 11 injections, healthier looking granulations, no further pain, able to use arm more fully;* end result unknown
2. Rumbold (4; 14; 23)	F adult	7 times recurrent round cell sarcoma rt. breast; (onset June 1892) final recurrence of rapid growth	1st operation July 1892 "non malignant;" recurrence in a few weeks; simple mastectomy; 2nd recurrence involved axillary nodes; very thorough removal summer 1893; 3 more operations for further recurrences	August 14, 1894; Coley MBV (Buxton VI) for 4 wks.	*complete regression by October 1894;* persistent nausea then occurred, due to internal metastases which caused death (date not given)
3. W.B. Coley (12; 14; 19; 23; 38)	F 42 at onset	ulcerated inoperable recurrent angiosarcoma lt. breast; onset following trauma; large 2nd recurrence extended from anterior axillary line to sternum, clavicle to ribs, fairly well fixed to chest wall, markedly protuberant; foul discharge; general condition very poor	fist-sized primary removed 1881; well 7 yrs.; egg-sized recurrence removed 1888; 2nd recurrence untreated; remains of growth excised September 18, 1895	February 1, 1895 Coley MBV (Type VII); 51 doses in 7½ mos., daily or every other day with intervals of rest; intense local inflammatory reactions but little febrile reaction; later 7 doses Buxton V (filtrate), less effective than serum	treatment caused hyperplasia of axillary nodes bilaterally; *slow, almost complete regression, growth much more movable, general condition improved; complete recovery;* in good health, no further recurrences; death from fall downstairs, 1903, 8 yrs. after MBV therapy, 23 yrs. after onset
4. Storrs & Griswold (2; 4; 5; 14; 18; 19)	F 42	inoperable rapidly growing spindle cell sarcoma breast & pectoral region, of very rapid growth (size of orange in 2	untreated prior to MBV; drainage established surgically to evacuate necrotic tumor tissue; sinuses irrigated with hydrogen peroxide	December 16, 1895; Coley MBV (Buxton VI) into tumor	*complete regression in 3½ mos., no recurrence; in good health; married; basal cell epithelioma on nose 1939; arthritis knees in later*

		mos.); rapid loss of weight & strength			*life; died arteriosclerosis and bronchopneumonia May 2, 1943, 48 yrs. after onset*
5. Nicholson (59)	F 58	twice recurrent inoperable spindle cell sarcoma lt. breast with extensive axillary metastases present at 2nd operation; 2nd recurrence 3 cm. in diameter; arm markedly edematous (onset March 1897)	primary removed 7 mos. after onset (1897); 2nd operation February 1898, mastectomy incomplete removal axillary nodes (indurated mass surrounded axillary vein); 2nd recurrence untreated	April 1898: Coley MBV (Buxton VI) given into recurrence 1–30 minims for 2 mos.	*recurrence disappeared in 2 wks., edema decreased; apparent cure;* alive & well when reported July 1899, 2½ yrs. after onset; not traced thereafter.
6. Shield (40; 64)	F 44	recurrent inoperable sarcoma of lt. breast, apparent 6 wks. after surgery in cicatrix, axilla, & beneath clavicle; overlying veins enlarged; large mass beneath pectoral muscle; pain radiating down arm	mastectomy January 1896 (axilla not involved)	April 3, 1896 Coley MBV (Lister Institute VIII); 1 minim into larger nodule; next day 2 m. in same lesion; then into clavicular metastases; febrile reactions to 103.8°F.; April 22, 1896 developed staphylococcus aureus infection, pustules on legs, petechial spots on abdomen (toxin used tested & found to be entirely sterile)	*pain greatly relieved at once; necrotic tumor discharged freely; in 10 days larger growth disappeared,* heavy, horny discolored patch of thickened skin; *smaller lesion semi-necrotic; mass beneath clavicle less prominent;* staphylococcus pyemia abscesses in liver, myocardium, kidneys, knee joint; caused death April 24, 1896; *all metastases had either disappeared or were necrotic at autopsy;* this is only case in nearly 900 treated by MVB who developed septicemia
7. Wentz (2; 4)	F 50	extensive inoperable recurrent sarcoma, primary in lt. breast, involving thorax below clavicle, practically immovable; pain radiating down arm, latter almost useless for 1 yr.; cachexia; (date of onset not recorded)	2 operations; "paste treatment" by quacks; collodaurum caused some improvement locally & in cachexia, collodaurum again given for 10 days in late June 1933	November 20, 1932 Coley MBV (Parke Davis XIII) into tumor & i.m. in hips, arms & breast near tumor, later deeply into tumor daily at first then every 2 days, then every 3 days; total duration over 7 mos.; reactions to 104°F., severe chills, treatment given as an outpatient	*growth became somewhat movable, gradual complete regression;* few mos. later evidence of recurrence; further treatment refused; death from multiple metastases, several years after onset

PART III, SERIES 5, SELECTED DETAILED HISTORY

CASE 2: Inoperable rapidly growing spindle cell sarcoma of the pectoral region and breast, confirmed by microscopic examination after operative biopsy by Dr. B.H. Buxton, Dr. E.K. Dunham of New York and by Dr. William H. Welch of Johns Hopkins.

PREVIOUS HISTORY: E.E.F., female, age 42, of New Britain, Connecticut. The patient's paternal grandmother had died of carcinoma of the breast. The family history was negative for tuberculosis or venereal disease. The patient's previous health had been good. Onset, she first noticed a hard lump below the left clavicle in the left pectoral and axillary region in October 1895. This grew rapidly and within two months had reached the size of an orange. It was firmly adherent to the deep vessels and extended well into the axilla. The general health deteriorated, and the patient lost 24 pounds in weight. She consulted Dr. M. Storrs early in December 1895. A consultation was held with McKnight, attending surgeon of the Hartford Hospital, and both surgeons regarded the condition as entirely inoperable. The patient was rapidly losing strength and weight. She was admitted to Hartford Hospital.

MBV THERAPY (BUXTON'S VI): Injections were begun on December 16, 1895 by Storrs. The initial dose was 1 minim, which was gradually increased to a maximum of 8 minims. The first chill occurred after the fourth injection on December 29, 1895. Injections were given every two days until February 8, 1896 during which time 39 injections were given, with 18 distinct chills. On February 9, 1896 a strong solution from more virulent cultures was obtained and the dose was reduced from 8 to 1 minim. However, this dose produced the most violent chill. This more potent solution continued to produce chills in doses of from 1 to 3 minims during the next five weeks when injections were given daily. The patient reported: "Chills came on 30 to 90 minutes after treatment, lasting from 30 to 45 minutes. When the newer stronger toxin was used I had the worst chill of all; with that toxin the chill would come on sometimes half an hour after the treatment. *The days I had a chill, I had less pain and felt better after the chill then the days when I had none. . .*" The patient did not take her temperature regularly, and the few times she did take it, half an hour after the injection, it was usually about 100°F. so the maximum febrile reactions in this case are not known, but are believed to have been about 103°F. to 104°F., judging by the general reaction. The tumor began to shrink shortly after the injections were begun. It was incised nine times during the course of the treatment, in order to facilitate drainage of the necrotic tumor tissue. The discharge increased after the more potent solution was used. All the incised areas were thoroughly syringed every time an injection was made for nearly three months. This was a painful process. During the treatment the patient's appetite was not very good, but she ate in order to maintain a little strength. The injections were given at home or at Storr's office after the first few treatments.

CLINICAL COURSE: By the latter part of March 1896 the growth had entirely disappeared and the patient had gained rapidly in weight and strength so that she soon regained the 25 pounds lost during the first two months after onset. Coley presented her before the New York Surgical Society on November 11, 1896, and also before the Clinical Congress

of Surgeons of North America on November 11, 1912. She remained in good health, married and when last traced by Coley shortly before his death, she was well except for rather painful rheumatism in her knees. In 1939 she developed a small basal cell epithelioma at the left side of her nose. She died on May 2, 1943 at the age of 80 of bronchopneumonia and arteriosclerotic heart disease, decompensated. This was over 47 years after onset.

REFERENCES: 2; 4; 5; 14; 18; 19

PART III, SERIES 6: ADVANCED INOPERABLE BREAST CARCINOMA TREATED BY A MIXED ENTERIC BACTERIAL VACCINE GIVEN ORALLY: 1 CASE

Since only one such case was found, it is given in detail:

DIAGNOSIS: Carcinoma of the breast with osteolytic type of secondary carcinomatosis involving the left iliac bone, the transverse processes of the lumbar vertebrae and the 12th rib, confirmed by clinical and x-ray examinations.

PREVIOUS HISTORY: Female, age 45. The patient was born in Scotland and was a physician living in Alexandria, Egypt. The early history was not recorded. Onset, late in 1942, she developed carcinoma of the breast.

SURGERY: A mastectomy was performed. Arthur Compton, M.D., D.Sc., then Director of Laboratories and Bacteriologist-in-Chief, Alexandria Municipality, Egypt, reported the case.

CLINICAL COURSE: Compton stated that by January 1945, the patient was confined to bed with sciatic pain following an attempt to get her home to Scotland from Egypt by plane. A radiological report from the third Military General Hospital on January 12, 1945, was as follows: "The osteolytic process in the left iliac bone is one which appears to have increased in area since last examination (beginning of spontaneous fracture). Changes are also seen on the transverse process of the lumbar vertebrae and the 12th rib. Osteolytic type of secondary carcinomatosis. No evidence of deposits in the lung fields."

VACCINE THERAPY: (Note: Compton had used a salmonella-coliform-guamaiform-phage preparation several years previously in a case of cancer of the liver in order to treat an intestinal upset. "The patient insisted that it relieved the symptoms of his cancer, and in consequence it was continued several months." This observation led Compton to use the same phage preparation in the present case.) Treatment was begun on February 16, 1945, and consisted in ingestion by mouth of two or three ampoules daily. On March 11th, three weeks after treatment was begun, the patient was able to be up in a chaise. Twelve days later she was able to get about with the aid of a cane. In another 10 days she demonstrated with pride what she could do in the way of movement of the left leg, something impossible a short time before. Almost from the beginning of treatment she was able to dispense with pain-easing drugs, morphine and aspirin, and in two months she was free from pain. On April 20, a roentgenological examination was made at the Institut de Radiologie, Alexandria, and reported as follows: "Formation of new bone at the margin of the ilium on the fracture line. The general aspect gives the impression that a certain amount of osteo-synthesis has taken place" since the last examination 14 weeks ago. The patient sailed for Scotland on April 21, 1945, and on the way home on the ship around Africa, the supply of the lysates gave out, and for seven days after her arrival she was without treatment. Compton stated: "Then she went on quite another type of lysate-preparation (an autogenous preparation) for five to six days."

CLINICAL COURSE: "This apparently gave no benefit, or may even have had an unfavorable effect. Pain returned and the condition rapidly deteriorated until she died on June 19th, two months after leaving Egypt in her greatly improved general condition, with the disease apparently under control." Compton added: "Incidentally, during the course of the

treatment a chronic psoriasis-like condition of the arms and legs of two years' standing, completely disappeared.'' In commenting on the case he stated: ''It did appear as if there was something in the bacterial lysate which had growth inhibitory and osteo-synthetic properties. Determination of the particular bacteria thus endowed entering into the make-up of the preparation, is a matter for future investigation, which I am anxious to undertake as soon as circumstances permit, in an attempt to understand what may be the meaning of the findings.'' (24)

Compton (1962–63) reported on the effects of feeding x-ray irradiated coliform bacilli in the drinking water to mice bearing a transplanted mammary carcinoma. He used 24 hour cultures of three different bacilli irradiated at 15,000 to 30,000 r. The growth of the tumor was retarded in 60 per cent of the animals, while in 100 per cent of the controls the tumors grew without interruption.

Compton suggested that these findings should be followed by more extensive experiments using different routes of administration, and trying to find the optimum dose of x-ray to use in killing the organisms and finally to attempt to isolate the protective substance responsible for the inhibitory effects. (24; 25)

PART III, SERIES 7:
METASTATIC BREAST CARCINOMA TREATED BY PREPARATIONS OF LACTOBACILLUS BULGARICUS (ANABOL):
6 CASES

Physician References	Sex Age	Diagnosis, Extent of Disease	Treatment Other Than Anabol	Anabol Therapy	Immediate and Final Results
1. Bogdanov (1a)	F 45	1968: solid scirrhus carcinoma rt. breast; undifferentiated adenocarcinoma lt. breast, metastasis to rt. supraclavicular region, pains in back, lt. leg, rt. arm, 1969; early 1979, general condition declined, loss of strength, anorexia, tumor nodules visible on *lt.* breast and rt. supraclavicular region	1/10/68: lt. mastectomy, oophorectomy; 8/4/69: biopsy lt. breast; palliative radiation to lt. breast and metastases—severe side effects, no benefit; further surgery refused	2/6/70: oral anabol begun, 10 grams daily for 22 mos., as only therapy	in 1 month general condition improved, pain and weakness disappeared, appetite improved, complete regression, NED, resumed full time job, alive & well 1/10/83, 15 yrs. after onset
2. Bogdanov (1a) (treated in Moscow)	F 42	carcinoma lt. breast, metastases to 2 lt. ribs, with pathological fractures, lt. ilium, rt. femoral neck. onset 1961, metastases occurred in early 1967; by June 1967, severe pain in ribs, back, pelvis, severe depression, weakness, restriction of movement	12/4/64: lt. mastectomy, radiation to ovaries, hormone therapy. 3/4/67: endoxan caused emesis, weakness, alopecia, leukopenia; no effect on metastases; 8/12/70 laparoscopy revealed miliary carcinomatosis of peritoneum; endoxan	9/6/67: oral anabol begun, 7–10 grams daily for 4 yrs. (only therapy) oral anabol continued during endoxan	gradual improvement during 1st month, complaints disappeared, gained 8 kg. in 3 mos. x-rays showed complete regeneration of normal bone structure in regions of metastases; complete remission lasted 32 mos. 8/12/70 ascites, continued despite therapy, death 1/20/72, 10 yrs. after onset, 4 yrs after anabol was begun
3. Bogdanov (1a)	F 47	adenocarcinoma rt. breast, metastases to parasternal lymph nodes and rt. lung, onset 1968	1/29/69: rt. mastectomy; 1/10/72: thyroidectomy for thyroid toxicosis	2/3/69: oral anabol begun, 7–10 grams daily for 2 yrs.	complete clinical remission of metastases, (seen on x-ray) gained 6 kg.; very good general condition, resumed her regular work, well 2 yrs., then weakness, exophthalmos, greatly enlarged thyroid; last traced NED 4 yrs. after onset

4. Bogdanov (1a)	F 61	1977: undifferentiated scirrhus carcinoma lt. breast, with axillary metastases; 3/9/78: lung metastases	10/1/77: pre-operative x-ray; mastectomy, axillary dissection; 3/9/78: cyclophosphamide & 5FU given under anabol protection; no evidence of regression of lung metastases until 7/79	10/1/77: oral anabol begun during x-ray; continued during chemtherapy, prevented side effects	WBC never fell below 5000 during chemotherapy, but lung metastases did not regress until 1979; very good general condition, and working capacity; NED by 1980; in good health 12/26/82, nearly 6 yrs. after onset
5. Bogdanov (1a)	F 60	adenocarcinoma rt. breast 10/31/78; pleural effusion, pleuritis developed 2 wks. after radiation, difficult superficial breathing, rapid pulse; 3/19/79: metastasis to frontal bone	no surgery; 10/31/78: x-ray (200kv, 2000 rads); 5 liters pleural exudate evacuated 2 wks. later; 10/78: i.v. & i.p. cyclophosphamide & i.v. 5FU; 3/19/79: 2nd course cyclophosphamide *tolerated without side effects* under anabol protection, at this time breast lesion 3 cm. in diameter; 3rd course given in O.P.D., no side effects	12/4/78: anabol given orally for 2 yrs; during 1980 brief periods of fever, reddening of breast	condition improved; remained in very good general health and working capacity; ''stationary tumor process'', 11/28/82, over 4 yrs. after onset
6. Bogdanov (1a)	F 40	scirrhus carcinoma rt. breast (onset 9/77); by 11/78 both breasts totally involved, metastases to pleura rt. pleural effusion	4/6/78: vincristine, dactinomycin, 5FU, methotrexate; no benefit, leukopenia, gastrointestinal intolerance; 2nd, 3rd & 4th courses given with anabol, caused no side effects; 6th course given without anabol, (vincristine, thiotepa, 5FU): side effects noted; loss of strength, anorexia, nausea, emesis, leukopenia (to 1050) thrombocytopenia (to 21,000); 7th course given under anabol protection; 8th & 9th courses given, well tolerated; by 7/27/79 WBC 5400, platelets 216,000	5/17/78: anabol begun, simultaneously with 2nd course chemotherapy; given orally for 14 mos. continued during 3rd, 4th & 5th courses of chemo; anabol reinstituted 11/78; 7th course given under anabol protection	tumor growth remained stationary until fall 1978, then growths extended outside mammary gland & involved pleura, with rt. pleural effusion; after anabol was resumed, general condition & blood picture improved in 10 days, pleural effusion ceased, lymphangiitis decreased; very good general condition 7/27/79; in clinical remission approximately 2 yrs. after onset

The next 3 cases indicate the protective effect of anabol when given concurrently with chemotherapy.

CONCLUSIONS

The end result studies cited above revealed the following significant findings which affected prognosis with this method and which were not readily apparent until our studies were made:

1. The marked variability of the 16 preparations of Coley Toxins.
2. The lack of recognition of the optimum technique of administration as regards site, dosage, frequency and expecially duration of injections. (See below Table 1 re duration.)

TABLE I

Duration of MBV therapy in Inoperable Mammary Carcinoma; Comparative Effects in Series 3 and 4

Immediate Results:	
Complete regression primary and/or metastases	
over 3 months treatment	52%
under 3 months treatment	0%
Marked or partial regression	
over 3 months treatment	28%
under 3 months treatment	14%
General condition improved	
over 3 months treatment	48%
under 3 months treatment	33%
Marked or complete pain relief	
over 3 months treatment	40%
under 3 months treatment	20%
Weight gain	
over 3 months treatment	16%
under 3 months treatment	8%
Little or no effect	
over 3 months treatment	16%
under 3 months treatment	41%
End Results:	
Traced well 5 or more years after onset	
over 3 months treatment	16%
under 3 months treatment	0%
Traced well less than 5 years	
over 3 months treatment	8%
under 3 months treatment	3%
Not traced, probably died	
over 3 months treatment	12%
under 3 months treatment	22%
Died of disease, survival not prolonged	
over 3 months treatment	20%
under 3 months treatment	70%

3. The stage of the disease: far advanced or terminal breast cancers in elderly patients, or in those whose immune responses had been destroyed or weakened by prior immunosuppressive therapy, produced very few permanent successes, although in many such cases significant palliation occurred.
4. The importance of timing as regards combination therapies: the best results occurred when injections were begun *prior* to surgery, irradiation or chemotherapy.
5. With inoperable cases, partial removal, by reducing the tumor burden may increase the percentage of permanent results.
6. When used as an adjuvant to surgery, injections should be started prior to excision or mastectomy, making some injections into the tumor or its immediate periphery to increase the inflammatory and immunological reactions in the tumor site.
7. Proteolytic enzymes such as varidase may now be evaluated in conjunction with bacterial vaccines.
8. The several mechanisms of action whereby microbial vaccines and enzymes exert their effects on breast cancer patients must receive much further study on an international cooperative scale, so that modern oncologists can use these agents to greatest advantage in the overall treatment of these patients, whose survival rate has not significantly improved in the past 80 years, with conventional modalities alone.

Since bacterial vaccines greatly increase the nonspecific resistance of cancer patients to infections, provided they are administered prior to the terminal stage, and since they promote wound healing, breast oncologists should now consider using them routinely before surgery, radiation or chemotherapy.

We have reviewed the results obtained with Coley MBT, since they mimic those seen at present with C. parvum or other immunotherapeutic microbial products and seem to have been more effective when administered correctly. These data may help avoid some of the mistakes made in the past as to technique, and encourage wider use of such agents at the present time.

Cooperative clinical trials should now be planned in many countries using carefully planned protocols for many microbial products alone or combined or used in rotation as immunopotentiators, not only in the inoperable breast cancers but also as an adjuvant to surgery, radiation or chemotherapy. The experiences outlined herein can offer useful guidelines in planning such studies and in avoiding the mistakes in technique which occurred in the earlier period before modern tumor immunology had been developed.

Prevention: The ultimate goal is the prevention of breast cancer as has been accomplished for polio through immunology. A few physicians who have routinely administered mixed bacterial or respiratory vaccines in treating infections, sinusitis, allergies or arthritis have observed a lower incidence of cancer in these patients.

These findings point the way to possible annual preventive courses of injections of microbial vaccines designed to maintain immunological responses at a proper level of efficiency, despite the effects of aging, stress or carcinogens in our environment.

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