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Hormonal etiology of carcinoma of the breast

Robert W. Gillespie
University of Nebraska Medical Center

THE HORMONAL ETIOLOGY OF CARCINOMA OF THE BREAST

By

ROBERT W. GILLESPIE

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INTRODUCTION

A French cynic once wrote that our ignorance of the therapeutic management of the menopause is largely responsible for the almost universal unpopularity of the mother-in-law. The introduction of the estrogens have solved this problem to some extent, but at the same time the average physician has been confronted with many problems as to its use and action.

Most recent of these problems is the relationship of the estrogens to mammary cancer. Experimental studies have shown that it is possible to produce mammary cancer in the rat on high estrogen dosage, but how are these results to be interpreted in human cancerology.

In the past ten years scattered reports have appeared in the literature citing cases of mammary cancer possibly induced by strenuous estrogen therapy. These reports, combined with editorial warnings by the Council on Pharmacy and Chemistry of the American Medical Association (21)(23)(62) on the prolonged use of the estrogens, have placed most of us in a state of confusion regarding estrogen therapy and hormone therapy in general.

It shall be the purpose of this paper, therefore, to review the experimental and clinical reports in an attempt to clarify the relationship of the estrogens to mammary cancer. In addition, a clinical report shall be presented on the menopausal age and cancer of the breast.

At this point I should like to express my gratitude and appreciation to Drs. Herbert H. Davis and John L. Gedgoud whose assistance and guidance have made this clinical report possible.

HORMONAL PHYSIOLOGY OF THE BREAST

"The breast must be considered a part of the female reproductive tract and as such is subject to the same stimuli throughout life as the other organs of reproduction".(51) The changes produced by the hormonal and other physiological factors on the breast are not uniform in their distribution. Nor will the same response to a hormone or group of hormones manifest itself in the breast of an adolescent and that of an adult. It will be beneficial, therefore, to consider separately the various stages in the development and involution of the mammary gland.

Experimental evidence is lacking to show that the embryological development of the breast is influenced by hormones. Development of the breast proceeds at the same pace in both male and female. Shortly before birth, however, the breast undergoes further development due primarily to the influence of the sex hormones, both placental and maternal. At birth, proliferation is noted in the ductal and periductal elements of the breast.

Adolescent development of the breast in the female is rapid in its course and is marked by extension and proliferation of the ductal system, hypertrophy of the

lining cells, and an increase in the periductal stroma. The nipple is found to be thickened and elevated beyond the contour of the breast. Lobule formation is conspicuously absent in this phase since it is dependent upon the action of the corpus luteum. Urine assays for estrogens are found to be elevated, indicative of an increasing estrogenic stimulus.

MacBryde was able to elicit a similar response, using estrogens locally in three cases of developmental failure of the breast with an inactive sexual cycle. In all cases the breast showed enlargement and fullness, and a vaginal smear exhibited an estrous phase.(49)

Estrogens are likewise responsible for the hypertrophy of the pre-pubertal breast in cases of granulosa cell tumors and account for gynecomastica in males with chorio-epithelioma of the testicle.

The adult breast undergoes changes which occur concommitantly with the hormonal fluctuations of the normal menstrual cycle. Lobule formation is present to some degree, dependent upon the follicular and corpus luteum hormones. It has been shown experimentally that the acinar structures may be developed by the singular action of the luteal hormone. A definite ratio of estrogen and luteal hormone is necessary to promote lobule

formation in cyclic women. FigureI. illustrates such a ratio based on estrogen and pregnandiol excretion in the urine.

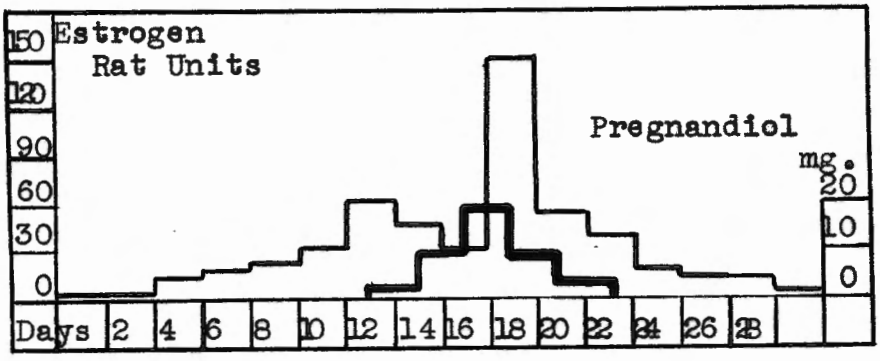

Figure I. Chart showing the recovery of estrogen and pregnandiol from the urine in a normal menstrual cycle. (After Geschickter, C. F.: Diseases Of The Breast, Philadelphia, J. B. Lippincott Co., 1943, p. 55.)

Geschickter reported a case of a 20 year old girl with a history of functional amenorrhea for three years. Biopsy of the breast revealed occasional rudimentary lobules in a dense fibrous stroma. Progesterone (145mg.) was administered over a six weeks period, following which, biopsy revealed numerous well developed lobules.(29)

The changes which occur during pregnancy are well known. These consist of: proliferation in epithelium and hypertrophy of the lobules in the first half of pregnancy, and further development of the acinar epithelium and distention of the glands following secretion in the latter half of pregnancy. Urinary determinations of estrogen and pregnandiol exhibit a steady rise to the

ninth month followed by a sharp decline at/or prior to parturition. During pregnancy, the placenta is the chief source of these hormones as evidenced by survival of the fetus following castration at various periods after the third month.

The acinar structure of the breast is very sensitive to deficiencies of the sex hormones. Postlactation changes are most marked since the ovarian hormones have been inhibited and the fibrous stroma has been crowded out by the numerous engorged glands.

Menopausal involution of the breast is characterized by the formation of minute cysts and dilatation of the tubules. Following, there is a gradual collapse of the tubules with involution of the epithelium and condensation of the fibrous stroma.(30)

The ovarian hormones which are present in unusual quantities during pregnancy are responsible for mammary proliferation, but inhibit the secretion and action of the lactogenic hormone. With the decline of ovarian hormones at birth, the inhibition is removed and lactation occurs.(55) The lactating breast shows dilatation of the ducts, actively secreting epithelium and increased vascularity. Lactation will not occur in a

breast in which there is incomplete development of the ducts and/or lobules. Geschickter points out that physiologic doses of estrogen prepare the mammary gland and also stimulate increased lactogen secretion by the pituitary. However, relatively high doses of estrogen over prolonged periods act to alter the response of mammary tissue to subsequent physiological stimuli.(35)

Experimental evidence has shown that section of the hypophysis results in failure to lactate or the immediate cessation of milk secretion.

In 1928, Stricker and Grüter demonstrated that a factor essential to lactogenesis was associated with the anterior pituitary. (63) Riddle and his co-workers, later isolated the factor in a sufficient degree of purity to demonstrate its independence from the growth and gonadotrophic and thyrotrophic factors.(64) There is no evidence that the development of the breast is assisted in the slightest degree by the lactogenic factor.

Robson demonstrated that the injection of estrogen into lactating mice inhibits the secretion both in normal and ovarectomized animals.(65)

Werner attempted to produce lactation in eight castrate women using injections of the lactogenic factor of the anterior pituitary. The breasts were pre-

viously prepared with injections of estrogen and progesterone, All patients experienced engorgement and enlargement of the breasts, however, none lactated.(76)

Tumors of the adrenal cortex in ovarectomized Bagg albino female mice produce as the dominant secretion either estrogen or androgen as judged by the microscopic appearance of the female reproductive tract.(26) It is through the dominant sex hormone secretion that mammary hyperplasia occurs, and it appears doubtful that hormones of the adrenal cortex are capable of producing mammary hypertrophy and hyperplasia.

EXPERIMENTAL STUDIES IN MAMMARY CANCER

Beatson,(6) in 1896, wrote: "We must look in the female to the ovaries as the seat of the exciting cause of carcinoma, certainly of the mamma, in all probability of the female generative organs generally and possibly of the rest of the body." This was the first implication of the hormonal factor in carcinoma of the breast. He based his theory on the histologic similarity between the lactating breast and a cancerous breast, namely dilatation of the ducts and epithelial proliferation.

Lett(45) nine years later, produced a series of 99 cases in which surgical oophorectomy had been undertaken as a palliative means of therapy. In his series, 36.4% of all cases were materially benefited by surgical oophorectomy.

In 1916, Lathrop and Loeb(44) demonstrated, experimentally for the first time, the significance of an internal secretion in the spontaneous development of cancer. They concluded from their studies: "Extirpation of the ovaries is in all probability effective because it eliminates the periodic growth of the mammary gland and allows it to remain in an uninterupted state of rest. But after

the mammary gland has been for a longer period of life under the influence of the corpus luteum, the threshold of growth processes which allows transition into a carcinomatous condition has been reached; hence, extirpation at later periods of life is found to be without effect."

Mechanism of Estrogen Activity

Susceptibility to cancer increases with the physiologic age of the breast rather than the chronological age. If accelerated development is maintained by prolonged stimulation the regenerating process of the tissues is ultimately exhausted. Atrophy of the gland occurs and it is in such a gland that further estrogenic stimulation results in benign and malignant tumors. "The essential feature in the estrogenic production of mammary cancer, therefore, is the acceleration or the prolongation of ripening and maturity in the mammary gland beyond physiologic limits."(36)

Geschickter produced mammary cancer in 202 of 555 rats of an albino strain which were treated with estrogens. The animals used had been inbred and spontaneous cancer had not been observed in a colony of more than 5,000 rats.(31)

LaCassagne has expressed a different view on the mode of action of the estrogens. He makes the hypo-

thesis that estrogen has been retained in certain regions of the mammary gland and has been able to exercise its proliferative action on the epithelium over a sufficient period to provoke cancer. In the human, it is known that colostrum contains a large quantity of estrogen, and this has likewise been shown in cystic cancerous breasts.(43)

He further postulates that the hormone is transformed by stagnation into one of the carcinogenic agents. It has been shown that the hydrocarbons and the sex hormones have one common denominator, namely the phenanthrene ring. By such a transformation, the action of estrogen is as a direct carcingenic agent.

In opposition to this theory, the following arguments have been raised: "One is that cancer does not occur at the site of injection but appears, instead, in the organ (the breast) which the hormone influences physiologically. The second is that the periods of time required to produce cancer with the estrogens of varying chemical composition are proportional to the physiologic potencies and independent of the chemical formulas. Therefore the estrogens cannot be considered chemically as carcinogenic agents."(32)

While little is known of the biochemical reaction through which the sex hormones produce their effect on the mammary glands, the changes in the tissue have been adequately described. (10)(11)(36)(49)(65)

Distinction may be drawn, histologically, in the action of the estrogens. In the first phase, or that of physiologic dosage, the ductal and periductal systems undergo hypertrophy and hyperplasia. In the realm of pathologic doses the gland undergoes atrophy and degeneration. Finally, there is a third effect characterized by atypical proliferation in epithelial and fibrous tumors followed by benign and malignant adenomas.

In order to study the mechanism of estrogenic effect, histologically, we must consider each phase separately and chronologically.

The earliest response to estrogen administration is evidenced by maturation in the ducts and tubules and proliferation in the lobular buds. This is the physiologic phase previously referred to. The duration of these changes will depend on the amount of estrogen administered. If the dose is physiologic, the changes noted will continue slowly; conversely, a pathologic growth results in a more rapid development and a shorter duration of this physiological phase of development.

More extensive dosage results in distention of the ducts and tubules with secretion, desquamation and atrophy of the lining cells and cystic formation of the lobular buds. This stage corresponds to mastodynia in the human breast.

The picture in the subsequent stage is that of degeneration and disintegration of the epithelial wall and fibrosis and sclerosis of ducts and tubules. In the lobular buds some cystic formation is still present. Rupture of the cystic wall together with basal cell proliferation may lead to cystadenoma.

Precancerous proliferation is next noted and the hyperplastic foci developed in the previous stages may continue to grow and develop into small neoplasms.

"In the breast, basal cell proliferation from the wall of the duct (which forms the lobular buds) is a form of regeneration which guards against exhaustion of the mammary epithelium when it is stimulated to over-ripening, secretion and desquamation by intense stimulation with estrogen...."(33)

Geschickter(34) has offered the following hypothesis on the origin of the malignant change; "Under ordinary circumstances a functioning tissue does not deplete its capital of reserve cells. The old cells...

are replaced by reproduction in the reserve colony.

In physiologic dosage, the ripening influence of estrogen on adult and maturing cells is compensated for by the stimulus exerted upon proliferation among the immature cells through the inter-relationship of these cells with the aging tissue....

The reserve cells of the tissue remain behind as reserve cells, because by virtue of biologic variation they are less susceptible to ripening effects than their fellow cells, and correspondingly more susceptible to division and multiplication in the immature state. Some of these cells of the reserve community, however, under the duress of intense hyperdifferentiation are subject to further ripening and development if the sitmulus is sufficiently intense. By this process of selection, only those reserve cells remain which are practically immune to developmental influences and which have an exaggerated propensity for reproduction.

In this way, any tissue approaching exhaustion because of an intense and prolonged differentiating influence has on hand a small but dangerous colony of cells, little influenced by developmental stimuli, but especially susceptible to influences which stimulate reproduction and divisiom. In other words, through hyperfunction and

hyperdifferentiation a tissue can be made to dip into its supply of reserve cells until by a process of natural selection only those cells practically immune to developmental influences and useful function remain.... These are the potentially cancerous cells."

Cramer(13) and others(22)(51) believe that the effect of estrogens on mammary epithelium is a quantitative one and that the carcinogenic effect is limited by other factors which may inhibit or enhance their action. Cumulatively, these factors may be termed "susceptibility".

Dosage and Intensity of Treatment

Suntzeff et al(68) found, after repeated experiments, that it was possible to increase the incidence of mammary cancer in mice by long continued injections of estrin. The effect varies directly with the size of the dose and the hereditary tendency of a given strain to develop cancer.

In high tumor strains of mice, large doses of estrin administered over long periods of time lower the age at which cancer appears below that at which tumors occur spontaneously. The cancer incidence is increased and the tumor age is lowered in high tumor strain mice

because of the great responsiveness of the mammary gland to prolonged stimulation with estrin.

It has been further shown that with daily injections of estrone in oil, the time elapsed before the malignant change is inversely proportioned to the dose. However, the total dosage remains fairly constant.

Intense interrupted doses of estrogen in female rats results in ripening of the acinar structures and cyst formation. With the appearance of cyst formation, the development of cancer is prolonged until atrophy and degeneration have taken place.

On the other hand, intense interrupted dosage in the female castrate rats results in hypertrophy and hyperplasia of ducts and terminal tubules. The malignant change is seen in these structures and not in the lobules.

Estrogen administered in the form of pellets results in the formation of fibroadenomas with a subsequent malignant metaplasia. Gradual continuous absorbtion of estrogen apparently results in the stimulation of the fibrous stroma to a greater degree than is seen with interrupted doses of estrogen in oil. Likewise, epithelial proliferation may predominate over ripening and secretion with the formation of duct adenomas and

intraductal papillomas.

In summary, therefore, it may be said that the quantitative expression of dose--response relationship cannot be definitely established from the available data. The malignant change in the breast varies with the methods of administration and the intensity of the dose of estrogen.

The Milk Influence Factor

"The studies on the extrachromasomal influences in the genesis of mammary cancer in mice culminated in the demonstration that at least one of the factors necessary for the occurance of these tumors was an agent, or agents, transmitted through the milk from mother or foster mother to offspring. In reciprocal crosses between high--and low--mammary--tumor strains, mammary tumors occurred in females whose mother belonged to the high--tumor strains. Foster nursing of mice of high--mammary--tumor strains by females of low--mammary--tumor strains reduced markedly the incidence of mammary cancer in the fostered females, and, conversely, foster nursing of low--mammary--tumor strain mice by mice that develop such tumors increased the incidence of mammary cancer in the fostered females."(67)

Bittner(7) states that at least three factors are essential for the production of mammary cancer experimentally: 1. An inherited susceptibility to the development of mammary tumors; 2. Hormonal stimulation of the breast, producing growth suitable for the cancerous alteration; and 3. An active mammary tumor milk influence which is transferred by nursing. All three factors must be present before carcinoma will appear. Male mice do not develop mammary cancer despite the presence of the genetic susceptibility and the milk influence, unless the lacking hormone factor is supplied. Quantitative deficiencies of one of the factors does not produce absolute resistance to the development of cancer; since this deficiency may be overcome by a relative increase in the other two factors.

In an extensive investigation in the genetics of human neoplasm, Martynova found that the percentage of cancer among relatives of patients with carcinoma of the breast was much higher than in the control population of the same age or among relatives of leukemic patients. The disease was 18 times more frequent in mothers of patients than in the control group. This alone speaks against a chance incidemce of heredity in the role of mammary cancer.(48)

The Effects of Other Hormones

Recent studies on the function of the adrenal cortex have shown that this gland contains steroids capable of both estrogenic and androgenic activity.

In recent years, Gardner(27) demonstrated that ovarectomy in mice at three to five months of age largely inhibited mammary tumors; while ovarectomy at five to seven months increased the incidence of tumors. An exception, but not an alteration to these findings, was the appearance of mammary tumors in ovarectomized mice at two to three months of age. In the latter group, the adrenals were found to be either hypertrophied or to contain tumors and the accessory genitalia showed evidence of estrogenic stimulation. He concluded from this study that the disturbance created by gonadal deficiency results in alteration in adrenal function and morphology and frequently the apposition of adrenal adenomas or carcinomas.

Frantz and Kirshbaum(26) demonstrated, further, that tumors of the adrenal cortex of castrated male Bagg albino mice secreted androgenic hormone, as evidenced by the histology of the seminal vesicles, submaxillary glands and renal corpuscles. They found that similar tumors occurred spontaneously in non-cas-

trate male and females of this stock, two years of age.

Cramer and Horning(14)(15) examined the adrenal glands of 95 mice belonging to sex different inbred strains for the presence of brown degeneration. Their results show a striking difference between the two inbred high--mammary cancer strains and all of the other strains (three cancer free and one low--cancer). In the former two strains, the degeneration began at an early age and after six months age it was present in all but one of each strain. In four other strains, it appeared at fourteen months and was not progressive. In the two high--mammary strains, the brown degeneration affected mainly the medullary cells of the gland.

This medullary degeneration differs from that produced by "oestrenized" non-inbred mice. In this group, the degeneration is found in the zona reticularis. Thus, two histologically different and functionally different types of degeneration are produced.

The spontaneous type of brown degeneration is not due to inbreeding per se; and it is not due to neoplasm, since degeneration may be found with or without tumor.

On the basis of their study, the following conclusions were drawn:

1. In the case of the two high-cancer strains, the susceptibility to breast cancer is associated with destruction of the medullary portion of the adrenal gland. In other words, an impairment of functional activity of the adrenal medulla favors the action of ovarian estrogen on the breast. Consequently, an antagonistic relationship exists between the medulla and estrogens and is, therefore, apposed to the cortical factor.
2. The disturbance of hormonal balance which occurs when a mouse of high--cancer strain develops a cancer of the breast spontaneously, is different from the development of carcinoma following excess administration of estrogen. In the high--cancer strain, the spontaneous development is not accompanied by an excess of estrogen. The pituitary gland also remains normal. The hormonal balance is disturbed only by the spontaneous brown degeneration, thus reducing the antagonistic factor to estrogen in mammary cancer.
3. The opposite significance is attached to the cortical type of degeneration with excess es-

trogen with its carcinogenic effect on the mamma. This leads to the cortical type of brown degeneration which in effect, diminishes the synergistic factor between estrogen and the adrenal cortex and represents, together with a change in the pituitary, an attempt to restore the hormonal balance.

Blaisdell(8), on the other hand, found brown degeneration to be the highest in three cancer resistant strains and was absent in many cancer susceptible strains which did develop cancer. Moreover, brown degeneration was never far advanced or medullary in distribution in any of the animals developing cancer.

"In order to restore the hormonal balance disturbed by the presence of excessive amounts of oestrin administered to the organism, the chromophil cells, and particularly the acidophil cells of the anterior lobe of the pituitary secrete their specific hormones. This stimulation to increased functional of the anterior lobe produces a hyperemia and hyperplasia of this lobe, together with a progressive degranulation of the acidophil cells which enlarge and assume the appearance of chromophobe cells. If the oestrinization is continued sufficiently long the process leads eventually

to an exhaustion of the anterior lobe, which is then greatly enlarged, deeply congested, and composed almost entirely of chromophobe cells." Working on this concept, Cramer and Horning(16) assumed that one or more hormones of the anterior pituitary are antagonistic to estrogen and possibly to the carcinogenic effects on the mamma. An investigation was then undertaken to determine the incidence of cancer of the breast in mice of the RIII strain treated with the thyrotropic hormone. All treatment was started before sexual maturity and in no cases did carcinoma appear. In a control group the incidence was 50%.

Therefore, we may conclude that excessive amounts of estrogen will produce a functional and histologic stimulation of the anterior pituitary culminating in exhaustion. In other words, estrogen administration produces a functional hypophysectomy.(12)

Clinically, variations in the size and consistency of the thyroid gland have been noted in patients with carcinoma of the breast.(70)

From the standpoint of human cancerology, the conception of an endocrine imbalance as an etiological factor in cancer of the breast should serve as a useful guide for clinical investigation. It has been

shown that pathologic alterations in the acidophil cells of the pituitary, in the human, have occurred in association with mammary cancer. Likewise adrenal cortical adenomas have been found.(13)

Adair has observed several cases of carcinoma of the breast in which the patient castrates herself by ovarian metastases and clinical improvement was noted until such time that the adrenals took over the ovarian function.(2)

THE HORMONAL ASPECTS OF HUMAN CANCER

Work on the experimental production of mammary tumors, previously described, has produced a great volume of literature and several useful theories on the mechanism of production of mammary cancer. However, the principle problem today is to find adequate evidence that the hormonal conditions present in women with cancer may resemble those produced artificially in the laboratory animal.

Methods of investigating the hormonal factor in the human, of necessity, must follow one of the following four courses: 1. Clinical history with special study on the menstrual cycle and related gynecologic aberations, 2. Histo-pathologic studies, 3. Clinical therapy and its effects on tumor growth, 4. Excretion studies of ovarian hormones.(73)

Age Incidence

Nathanson(54) in a study of 2,165 cases of cancer of the breast, found the peak of age incidence was reached in the age group between 46 and 48 years of age. In this series, one third of the cases occurred before age 45, another third between 45 and 55, and the remainder above age 55. McDonald(47) and Pack(59) quote similar results in a study of 2,531 patients with malignant tu-

mors of the breast. When the incidence in the general population is considered, it has been shown that susceptibility to breast cancer increases steadily with age.

McDonald(47) feels that the classical description of the menancing course of breast cancer in the young should be stricken from the text books as a misconception. In his series, five year cures were experienced in 10 of 13 cases under 25 years of age. Furthermore, there was a slight but persistant percentage excess of five year cures over recurrent cases in the age period of 36-50 years.

Lactation

Experimental studies previously referred to, indicate that a lactogenic and a milk influence factor play a major role in mammary carcinogenesis. It is well known that nulliparous women have a higher incidence of mammary cancer. This is in direct opposition to the experimental results in rats. McDonald(47) and LaCassagne(43) feel that early weaning of the child or faulty lactation leads to the development of breast cancer; based on the supposition that atypical lactation results in stasis and the breakdown products of the hormones present may have a direct carcinogenic effect.

Taylor(72) investigated the feeding history of

350 children of women with breast cancer. He found that 72% of the children were nursed for at least six months and of the remainder, a small number were deliberately weaned and others were not nursed because of inadequate milk supply. He feels that further studies are necessary and may reveal an inflamatory state resulting from stasis or an alteration in the physiologic response of the breast leading to a predisposition to mammary cancer.

Coincidence of Breast and Uterine Cancer

Taylor in 1931(71) reported 18 cases of uterine cancer coincidental with primary breast cancer. In his series, the average time elapsed between the two neoplasms was 16 months. Recently, Pierce and Slaughter(61) found three cases of malignancy in the cervix, ovary, and uterus (one of each) following routine gynecologic examination of patients with breast cancer. These findings indicate the presence of a common denominator, namely the estrogens.

Effects of Castration

Beatson(6) was the first to describe the effects of castration on mammary cancer. In his description improvement was noted in soft tissue metastases and the general well being of the patient.

Later, Lett(45) reported improvement in 36% of 99 cases of inoperable carcinoma of the breast treated by surgical oophorectomy. He stated that the most favorable age period was 45 to 50 years and should be given favorable trial in the younger age groups.

Herrell(38) reviewed 1,906 cases of mammary cancer and found that the incidence of complete oophorectomy or castration before cancer was diagnosed, was 1.5%. The incidence in a control group was 15% or 10 times as great.

Adair and his group(2) recently published the results of castration in 335 cases of mammary cancer in females. In this series 15% were definitely improved, 19% were grouped as uncertain as to improvement and 66% were not improved by castration.

Carcinoma Coincidental With Estrogen Therapy

Allaben and Owen(44) were the first to describe a case of mammary carcinoma coincidental with strenuous endocrine therapy. In this case, the patient received 250,000 units of injected estrogen over a 14 month period prior to the discovery of the tumor. Auchinclos and Haagensen(5) described the histological findings in a similar case of breast cancer preceded by strenuous estrogen therapy. The carcinoma in this patient was of an unusual histologic type, characterized by ductal

dilatation with low cuboidal epithelium and cystic formation, and a well differentiated carcinoma with small irregular acinii. The dilatation of the ducts and epithelial proliferation were similar to that found in other human breasts following strenuous estrogen therapy.

Other reports(60)(75) of a similar nature have appeared in the literature; it is of interest to note that all patients reported were between 40 and 50 years of age. Further definite proof must appear before implication of the estrogens can be made clinically.

The Effects of Hormone Therapy

The effects of various hormone preparations on the course of mammary cancer has been the subject of numerous investigations.(9)(52)(74)(40)(7)(38) Collectively, their effects may be summarized as follows: 1. Estrogenic substances (diethylstilbesterol, ethinyl estradiol, and estrone sulfate) may produce some beneficial effects on the primary lesion and also on the extra-skelatal metastases. Pain, the most common symptom, was relieved in a high percentage of cases. 2. The degree of retardation obtained was much less than could be expected from palliative irradiation. 3. The favorable results are confined to the older age groups, in the younger women

there were no benefits or the effects were detrimental. 4. Androgenic therapy affects, beneficially, the osseous metastases. The lesions are found to recalcify and pain is eliminated. 5. Androgenic hormones do not inhibit the formation of new osseous metastses.

Liver Function and the Estrogens

Glass, Edmonson, and Soll(37) studying estrogen excretion in 14 males with chronic liver disease noted the presence of total free estrogens in the urine in eight cases of hepatic cirrhosis. In all eight cases gynecomastica was noted. They concluded that the cirrhotic liver fails to inactivate estrogens and consequently free estrogens are present in the blood in abnormal amounts. Tagnon and Trumell(69) found that the incidence of abnormal liver function tests was high in a group of 27 cases of operable breast cancer.

Excretion Studies

Estrogen determinations in cancer of the breast have been relatively scarce, and in general, the results have not been startling.

The estimation of hormones in urine shows that the hypofunction of the ovaries at the menopause is due to a primary condition in the ovary is not secondary to hypofunction of the anterior pituitary. There are two

pronounced changes in the hormonal pattern at the menopause: hypoestrinism and increase in the follicle stimulating hormone excretion.(3)

Nathanson, Rice and Meigs(53) found surgical and x-ray castrate patients undergo similar changes in the hormone pattern.

Frank et al(24)(25) studied the hormone excretion in 52 menopausal women. In at least 50% of the cases after the menopause, and including surgical castrates, considerable quantities of estrogenic factor were found circulating in the blood and excreted in the urine.

Murphy and Fluhmann (50) found estrogen present in 13 of 21 post menopausal women, in a cyclic form. 5 other patients showed a constant amount of estrogen, while 3 were negative.

CLINICAL REPORT: THE MENOPAUSE AND MAMMARY CANCER; A STATISTICAL SURVEY BASED ON 384 MENSTRUAL HISTORIES.

The menopausal age has been an incidental recording in several statistical surveys on mammary cancer, but seldom has it been thoroughly investigated.(56)(77) The principal reason for this lack of investigation has been, I believe, the confusion in the term menopause. In reviewing several histories on the same patient, one is often confronted with wide variations in the recorded age of the menopause. The menopause may mean to one person the absolute cessation of the menses while to another it denotes the onset of irregularity and diminution in the menstrual flow. In this study, the menopause shall be recorded as the complete and permanent cessation of the menstrual flow.

Table I presents a division of the cases in this study into three groups: Group A, the breast cancer series consists of 160 cases of breast cancer in the University of Nebraska hospital over a 12 year period. No case was used for this study in which castration either by surgery or x-ray had been performed before the normal cessation of the menses; Group B, has been designated the extra-genital cancer series and consists of

59 cases in which a diagnosis of malignancy outside of the breast and genital system was made. The third group (Group C) consists of 165 consecutive admissions to the University hospital. Qualifications for the latter group required only that the women had passed through a normal menopause, as defined above, and the absence of a malignant condition.

TABLE I.

GROUPS	NUMBER OF CASES
A. CANCER OF BREAST	160
B. EXTRA-GENITAL CANCER	59
C. NON-MALIGNANT CASES	165
TOTAL	384

Results

The age incidence of the cases in the breast cancer series are recorded in Table II. It will be seen that the incidence has been recorded under two headings:

1. The age of onset of the neoplasm as judged by the

the discovery of the mass in the breast. 2. The age at which the patient was hospitalized for treatment.

TABLE II.

AGE INCIDENCE OF MAMMARY BREAST CANCER

AGE PERIOD (yrs)	AGE OF ONSET	AGE AT HOSPITAL
30-39	13	9
40	2	3
41	3	3
42	4	1
43	2	2
44	3	4
45	5	4
46	7	6
47	3	4
48	7	4
49	8	6
50	4	9
51	4	3
52	4	7
53	3	2
54	7	4
55	5	3
56-60	20	25
61-70	38	46
71+	18	20
TOTAL	160	160

In the first column (age of onset), 103 cases or 64.3%, the neoplasm appeared at 50 years of age or later.

In the second column, 74.4% of the patients were in the age group 50 years or over indicating a considerable lapse of time from the onset of the tumor until treatment was begun.

The menstrual status at the time of onset of breast cancer has been recorded in Table III. It was found that the menses were regular in 57 cases (35.6%) at the time the mass was discovered; in only 9 cases were the menses regular in the age groups past fifty. Menses had ceased before the onset of the tumor in 103 cases (64.4%) of which, 9 cases were in the age group 30-49 years. In other words, normal cyclic estrogen stimulation of the breast was present in a little over 1/3 of the patients in this series at the onset of the malignant process.

TABLE III.

DETERMINATION OF THE MENSTRUAL STATUS AT THE TIME OF DISCOVERY OF BREAST CANCER.

AGE GROUPS	MENSES REGULAR		MENSES CEASED	
	NUMBER	PERCENT	NUMBER	PERCENT
30-49	48	30%	9	5.6%
50-71	9	5.6%	94	58.8%
TOTALS	57	35.6%	103	64.4%

Table IV presents an analysis of the manopausal ages in the three groups under consideration. In Group A, 112

TABLE IV.

AGE INCIDENCE OF THE MENOPAUSE

AGE	GROUP A.	GROUP B.	GROUP C.
35	0	3	2
36	0	0	0
37	0	0	3
38	1	1	0
39	2	0	2
40	3	8	3
41	1	1	3
42	5	3	10
43	1	1	6
44	1	1	7
45	8	8	12
46	6	0	12
47	3	3	10
48	8	1	15
49	12	2	13
50	23	10	32
51	4	3	11
52	12	3	10
53	7	1	4
54	8	4	2
55	2	1	6
56	1	0	0
57	0	0	0
58	2	0	1
59	0	0	0
60	1	0	0
61	0	0	0
62	0	0	1
TOTAL	112	54	165

patients had passed through the menopause and 48 patients were still menstruating. The mean age in this group was 48.93 years. In the extragenital cancer group, 59 cases were recorded of which 5 were menstruating regularly. The mean age in this group was 46.99 years. Group C consists of 165 patients, all of whom had passed through the menopause; the mean age being 47.63 years.

The incidence of regular menses in Groups A and B are recorded in Table V. 9 cases in the breast cancer group were found to have regular menses in the age group 50-56. Of the five cases in Group B, none had reached the age of 50.

TABLE V.

AGE INCIDENCE OF REGULAR MENSES IN GROUPS A AND B.

AGE GROUPS	GROUP A.	GROUP B.
39	10	0
40	3	0
41	3	0
42	0	0
43	2	0
44	4	0
45	4	0
46	5	0
47	2	2
48	4	2
49	3	1
50	4	0
51	1	0
52	2	0
53	0	0
54	0	0
55	0	0
56	1	0
TOTALS	48	5

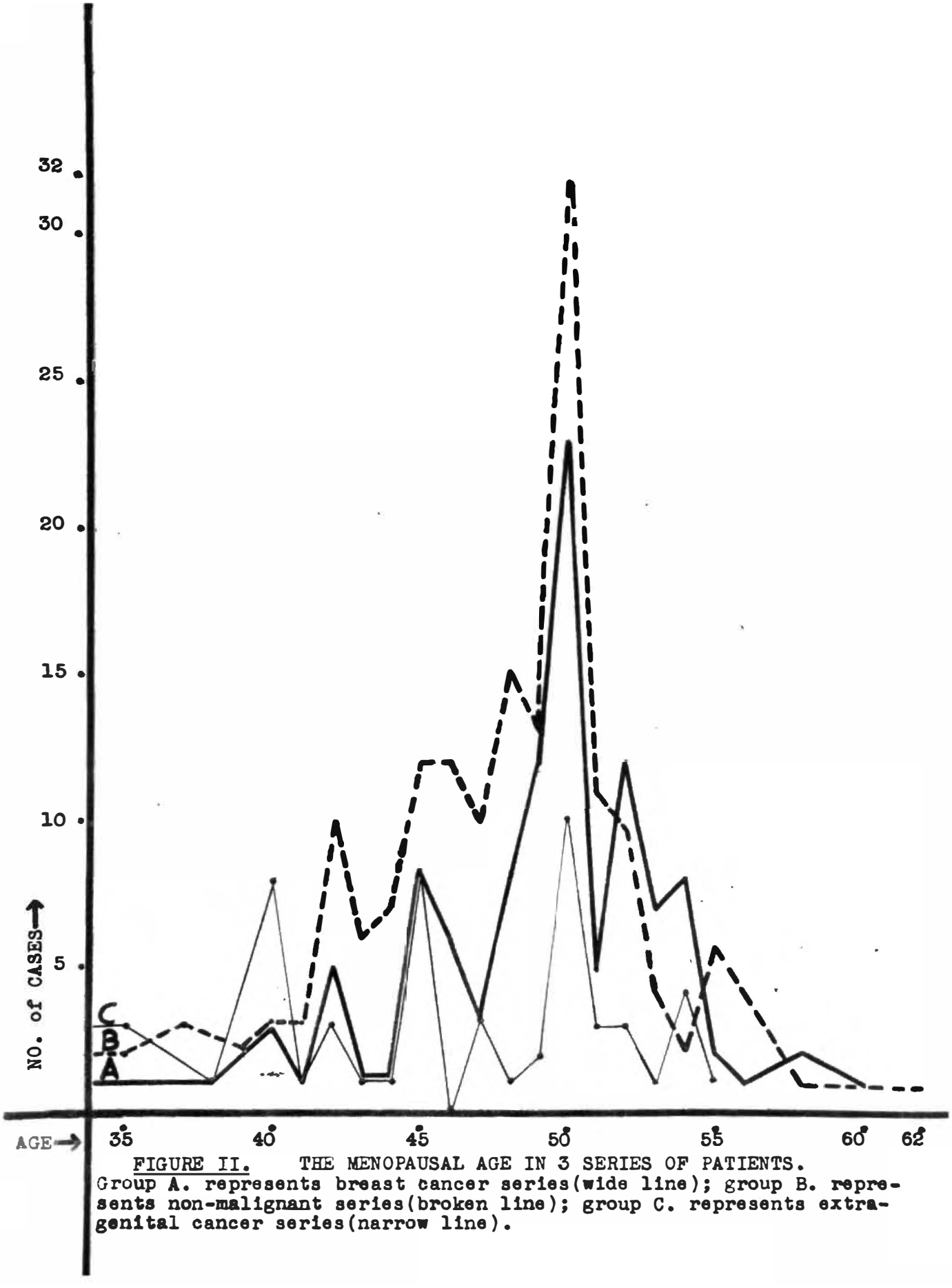

FIGURE II. THE MENOPAUSAL AGE IN 3 SERIES OF PATIENTS. Group A. represents breast cancer series(wide line); group B. represents non-malignant series(broken line); group C. represents extra-genital cancer series(narrow line).

Figure II illustrates graphically the menopausal age incidence in the three series. The peak of age incidence in each group was age 50.

In the breast cancer series, 43.1% (69 cases) of the patients were still menstruating or had ceased menstruating at or past age fifty. The menopause did not occur until 47 years or later in 52.5% of the cases. The menopause did not occur until 50 years or later in 37.2% of the patients in the extra-genital cancer group.

67 cases (40.6%) in the non-malignant group ceased menstruating at or past 50 years of age.

It was interesting to note that uterine cancer had been diagnosed coincidentally in two cases in the breast cancer series. An adenocarcinoma of the uterus was diagnosed in one patient, one year prior to the discovery of the breast tumor. The carcinoma in the uterus was confined to the endometrium. The second patient had had a previous diagnosis of carcinoma of the cervix 6 years prior to her breast cancer.

Discussion

The age incidence in this series of breast tumors is slightly higher than that found by other investigators. (54)(59)(47) In discussing age incidence, one is ever conscious of the "cancer age". The acceptance of

the middle and later ages as the "cancer age" does not pass without its pitfalls; every investigator studying the age incidence of cancer has been faced with a small but persistant number of cases in which the neoplasm had occurred before the "cancer age". In reviewing all breast cancer cases in the University of Nebraska hospital over a 12 year period, it was found that in the patients under 40 years of age an average of 16.8 months had elapsed from the onset of the tumor until treatment was begun. Certainly in this "cancer minded age" we cannot contribute this delay solely to ignorance on the part of the patient. We should bear in mind, therefore, that regardless of age, "Every single solid lump in the breast should have an immediate biopsy".(19)

Olch(58) in 1939, investigated the menopausal age in 342 women with cancer of the breast. In his series, he found that 50% of the women discovered the lump after age 50 and many of these women were still menstruating. Investigating the menstrual history in these patients, he found that 54.7% were still menstruating or had ceased after 50 years of age. This was five times as many as in a normal series. He raised the question as to whether we are justified in producing an irradiation castration in healthy women or in women who harbor chronic

cystic mastitis, who have passed the age 48 to 50 without a menopause.

Dawson(20) found that the peak incidence of the menopause in 300 cases of cancer of the breast was age 51.

Wevill(77) in 1932, determined the age of the menopause in 142 cases of cancer of the breast to be 48±2.

The average age of the menopause as based on the last menstrual period on a series of 200 healthy patients was found to be 47.89 years; the peak incidence of this series was 49 years of age.(57)

Crossen and Crossen(17) wrote regarding the age of the menopause that "Suspicion of abnormality should be aroused by menopause occurring before age 42 or delayed to the age of 48 years, and the greater the variation below or above these limits, the greater the probability of some pathological process.".

Crossen and Hobbs(18) found that the menopausal age was past 50 years in 50% of a series of 89 cases of adenocarcinoma of the uterus. On the basis of their findings, they advised the use of radium castration in any case menstruating after 50 years. They feel that such late menstruation is a definite indication of a tendency to endometrial malignancy.

The results of this investigation do not confirm the findings of previous investigators(58)(20)(18) in the menopausal age in cancer of the breast. Although, the number of cases in this series is small, the results are statistically significant. On the basis of the following results in this study, I find no real indication for castration of healthy women (or those with cystic disease of the breast) who have menstruated past 50: 1. The peak age incidence in the three groups was 50 years of age. 2. There was no significant variation in the percentage of patients in any group that were still menstruating or had ceased menstruating at or past 50 years of age. 3. The mean age in the three groups varied from 48.93 years in the breast cancer group to 46.99 years in the extra-genital cancer group. 4. Of 160 patients with mammary cancer, only 9 cases or 5.6% were found in the 50-71 age group in which the menses were regular at the onset of the neoplasm.

In conclusion, therefore, the need is apparent for further investigation on the part of the clinician, chemist, endocrinologist, and pathologist to establish the relationship of the estrogens to mammary cancer and malignancies of the genital system as a whole.

SUMMARY

1. A discussion of the hormonal etiology of carcinoma of the breast is presented from both experimental and clinical viewpoints.
2. A clinical report has been presented on the age incidence of the menopause in breast cancer patients.
3. Menses were regular in 35.6% of the patients at the onset of the breast cancer.
4. The peak age incidence in the three groups under consideration occurred at age 50.
5. The mean age in each series did not vary more than 1.94 years.
6. A similarity was found in the percentage of patients in which the menopause occurred at or past age 50 in the three groups underconsideration.
7. On the basis of this report, no indications were found to warrant the castration of healthy women who are menstruating after age 50.

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