THE EVIDENCE FOR AN ENDOCRINE FACTOR IN THE ETIOLOGY OF MAMMARY TUMORS

HOWARD C. TAYLOR, JR., M.D.

To present the evidence for an endocrine factor in mammary tumors requires a survey of several fields of investigation, pathologic, experimental, and clinical. Of these, the last will be stressed in this paper. In particular an attempt must be made to bring certain clinical aspects of the problem into closer relation with laboratory research.

I. THE NORMAL BREAST

The endocrine origin of breast tumors rests on the hypothesis that the stimuli to normal growth, when active in increased intensity or applied over excessive or irregular periods of time, may result in atypical forms of proliferation. For that reason the facts of the hormone physiology of the normal mammary gland are of basic importance in the study of breast neoplasms.

A. Experimental Physiology: The dependence of the normal growth and development of the female mammary gland upon the ovary is perhaps the central fact of breast physiology. It was indicated first by castration and implantation experiments, and is now easily demonstrable by the injection of the estrogenic hormone into laboratory animals. That the mammary rudiments of male animals are likewise responsive to the ovary was also shown many years ago by implantation experiments, and the effect of the injection of estrogenic hormone on the male mammary gland of many animals is now well known. Recent reports of the enlargement of the breasts of women with a low or absent ovarian function following the injection of the estrogenic hormone (Werner and Collier, Loeser) add to the evidence that the human breast is also basically dependent on the ovary.

It was first maintained that with the estrogenic hormone alone epithelial proliferation equal to that of pregnancy could be produced. Certain limitations and complications have, however, appeared. In the first place, evidence has accumulated to show that a definite limit is reached (Vitemberger, Parkes, Turner and Frank) beyond which greatly increased amounts of estrin are incapable of producing a further physiologic effect. Other experiments suggest that estrogenic substances of different chemical composition act specifically on particular parts of the mammary gland. With certain compounds Burrows noted in mice an extension of the duct system with little development of acini, while with others the appearance of new acini was the prominent change. Similar experiments by Gardner, Smith and Strong showed that,

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when oestrone benzoate was injected subcutaneously into male mice, there resulted not only a stunted development of the mammary duct system, as compared with that induced by small daily injections of theelin, but a growth of well formed lobules of alveolar tissue.

As the cause for the development of the mammary gland beyond the stage produced under physiologic conditions by the follicular hormone of the ovary, two additional hormones must be considered, those of the corpus luteum and the anterior pituitary. A relationship between the corpus luteum and breast hyperplasia has long been accepted as a result of the classical observations of the development of the breasts in the pseudopregnant rabbit (Bouin and Ancel, Asdell and Salisbury). Turner and Frank have more recently described the development of true acini when corpus luteum hormone was given after the estrus-producing hormone had produced only duct development in the castrate male rabbit. As a result of this observation a theory has become widespread among some clinical pathologists that duct hyperplasia is the specific effect of the follicle hormone, acinar hyperplasia of the corpus luteum, but present evidence seems insufficient to permit any general acceptance of so nice a division of function. Other observations have, in fact, been made of breast development up to the stage of lactation in the complete absence of luteal influence, as in male animals treated with estrogenic hormone (Nelson and Smelser). The special relation of the corpus luteum to the breast must be regarded as still undetermined. Its importance probably varies greatly in different species.

The function of lactation is a process quite distinct from that of development and is dependent on a different set of glandular relationships. It is true that a little milky fluid has been reported after the long continued injection of estrin in certain animals, but the sudden diminution in supply or the withdrawal of this substance results in a considerably increased secretion (de Jongh and Laqueur). Conversely, when lactation is once established, the secretion may be reduced by the administration of the estrogenic hormone (Parkes and Bellerby, de Jongh, Smith and Smith) or by substances which themselves stimulate the ovary, such as the gonadotropic hormone of the anterior pituitary (Enzmann and Pincus).

That the anterior pituitary is the active stimulus to lactation has been demonstrated by a series of injection experiments begun by Stricker and Grueter upon rabbits and continued by a group of other workers (Evans; Asdell; Donahue; Gaebler; Lyons and Catchpole). Agreement exists, however, that the parenchyma of the glands must be prepared by the developmental stimulus of estrin before the functional stimulus of the anterior pituitary can be effective. This relationship has been demonstrated on several laboratory animals, but attempts to induce lactation in castrate women by the use of these hormones have not been entirely successful (Werner).

That the anterior pituitary is essential to milk secretion has been further demonstrated in a series of experiments showing that lactation cannot occur or continue in hypophysectomized animals (Selye, Collip and Thomson; Allan and Wiles; Pencharz and Long; Lyons and Pencharz; Lyons, Chaikoff and Reichert; Nelson).

Finally a specific lactogenic hormone has been isolated from the anterior
pituitary, first by Riddle and his co-workers and later by other investigators (Gardner and Turner; Nelson). Injections of this substance, termed prolactin or galactin, have been shown to cause milk secretion even after removal of the ovaries or the pituitary (Lyons, Chaikoff and Reichert). The specific nature of this hormone is shown particularly by the fact that lactation has been produced in monkeys following its injection without histological changes in the other organs of the reproductive tract (Allen, Gardner and Diddle).

B. Hormone Physiology of the Human Breast: In attempting to apply the data derived from laboratory experiments to human breasts, one has to explain numerous facts already long the object of speculation by clinicians. These include the swelling of the breasts of the new-born, mammary development at puberty, the cyclical premenstrual enlargement, the hypertrophy in pregnancy, and the continuation of lactation during the nursing period. Studies of the blood concentrations and rates of excretion of the hormones of the ovary and anterior pituitary, made possible by the Aschheim-Zondek and Allen-Doisy tests, have been of great aid in relating these manifestations to the facts of animal research.

(a) The swelling and secretion of the breasts of the new-born coincide with a demonstrable excretion of large quantities of estrin and prolan (Philipp; M. Frank; Brühl; Neumann; Winter). Histologically this early hyperplasia has been considered to resemble certain of the abnormal hyperplasias of later life (Cheatle). It is unquestionably the result of the stimulus afforded by the maternal hormones which reach the fetal circulation before birth and are gradually excreted thereafter. A rapid involution of the infantile breasts follows the disappearance of these substances from the urine.

(b) In childhood the blood and urinary concentrations of estrogenic hormone are apparently low, although small quantities of gonadotropic substances have been reported (Schörcher; Soeken; Zondek and van Euler; Freed; Neumann). The breasts and uteri are actually smaller at two years of age than at birth. Precocious breast development has been repeatedly reported, however, in the presence of certain specific ovarian neoplasms, the granulosa-cell tumor (R. T. Frank; Novak; Pahl; Bland and Goldstein), and the teratoma (Siegmund; Bettinger; Fasold). In the former type an excessive excretion of estrin and in the latter of prolan have been demonstrated.

(c) Studies of the hormone changes preceding puberty are incomplete. It is of considerable significance, however, that breast development begins at the tenth year and has progressed to a considerable extent before the first menstrual period. With the regular recurrence of the follicle-corpus luteum cycle, as evidenced by the menstrual periods, a condition of relative stability in the mammary gland is arrived at. The degree of development thus attained at puberty, however, varies greatly in different individuals, resulting in glandular structures of varying complexity (Dieckmann) and probably physiologic potentiality. Such differences are perhaps the basis of variations in the later responses of the breast to the stimuli of the menstrual cycle and pregnancy and perhaps to the factors favoring abnormal growth.

(d) The nature of the changes taking place in the breast in relation to the menstrual cycle has been the subject of considerable controversy. The matter is of some importance because of the widely held clinical theory that
certain forms of chronic mastitis are based on disturbances in a normal cycle of proliferation and regression of the mammary epithelium.

The cyclical changes in the blood concentration and the rates of urinary excretion of the hormones which might theoretically be responsible for breast reactions have been carefully studied. In the blood there is a curve of estrin concentration probably reaching a maximum shortly before menstruation (R. T. Frank), although other workers have noted less regular variations in concentration (Fluhmann; Ford and Mueller). In the urine a cycle of estrin excretion has also been noted, certainly with low levels for ten days following menstruation with somewhat irregular curves thereafter (R. T. Frank; Siebke; Taylor). Peaks in urinary excretion and in blood concentration of gonadotropin hormone have been reported in the intermenstruum near the time of ovulation (Frank and Salmon; R. T. Frank; Kurzrok; Katzman and Doisy). The presence of corpus luteum hormone in the blood may perhaps be assumed at the time of the maximum development of this structure in the ovary, but a cycle in the blood or urine is not demonstrable by any accepted tests.

The days of breast enlargement, tenderness, and hyperemia fall in the premenstrual part of the cycle and correspond, therefore, with a high level of estrin and presumably corpus luteum hormone in the blood stream. The days when the gonadotropin hormone is detectable in the blood and urine correspond to a phase of apparent inactivity in the breast.

The conflicting views on the cycle of histologic changes in the human breast have recently been reviewed (Taylor). With the accumulation of evidence the theory of a monthly cycle of epithelial proliferation and regression becomes less and less tenable.

(e) The relation of the pregnancy hypertrophy of the human breast to the hormones is easily demonstrable. As is well known, an anterior pituitary-like hormone appears in the urine within two weeks of conception, increases in concentration until about the fourth month, and then gradually decreases until the end of pregnancy (Zondek; Smith and Smith). Estrin in large amount appears somewhat later and increases slowly in its concentration in blood and urine until term. During the first three to four months the corpus luteum of pregnancy is present, but thereafter regresses. Under the influence of these three hormones the epithelium of the breast undergoes enormous proliferation. A little secretion of a special type occurs during the latter months of pregnancy, but no true lactation.

During the first few days after delivery the prolan and estrin disappear from the blood and urine, and lactation commences. Excessive amounts of estrogenic or gonadotropin hormone are not detectable in the blood at this time, so that lactation in women appears to be favored, as certain of the older animal experiments suggested, by a sudden drop in estrin concentration. A special lactogenic hormone of the anterior pituitary may be active, and has in fact been demonstrated in the urine of lactating women (Lyons and Page). Furthermore, an increase in lactation has been reported after the administration of prolactin to lactating women (Kurzrok, Bates, Riddle, and Miller). The importance of the nervous stimulus afforded by the act of suckling to
the continuance of lactation is, however, obvious to any clinician and is receiving increased attention in laboratory research (Selye, Collip, and Thomson).

(f) The end of menstrual life is accompanied by a disappearance of estrin from the blood and urine and a definite increase in anterior pituitary activity. Under this régime there is a more or less rapid shrinkage of the breasts and disappearance of the glandular elements. The process is not usually a regular one, however, and in the uterus, for example, is often accompanied by prolonged bleeding suggestive of abnormal hormone activity. In the breasts cessation of the menstrual periods may be associated with the secretion of a little milky fluid, and the atypical epithelial structures found at this age are perhaps the result of the irregular hormone stimuli (Allsberg; Grünbaum; Ebeler; Litten; Cohn).

II. THE ENDOCRINE FACTOR IN ALLIED TUMORS IN THE PELVIS

The similarity of the physiology of the breast to that of the uterus suggests that much help in the study of mammary neoplasms might be obtained by reference to work already done on the etiology of female pelvic tumors. The existence of a common hereditary tumor of the mammary gland in mice has indeed given this organ precedence in the laboratory study of the endocrine factors in tumor development. This is not, however, true in the clinical field, where the best opportunity for correlating tumor development with evidence of ovarian dysfunction is found in the female pelvis. A glandular factor in pelvic neoplasms has in fact been a familiar conception for many years, and it is with some amusement that many gynecologists have looked upon the enthusiasm with which the general surgeon has fallen upon the endocrine theory of breast neoplasms. Two examples will suffice:

(a) Hyperplasia of the endometrium was first referred to an ovarian disorder by Brennecke in 1882, and since 1915 has been regarded as the result of a persistent ovarian follicle and an absence of corpus luteum. The conception has had some modifications, but the basic relationship has remained unaltered. High estrin values in blood and urine have been demonstrated in patients with this condition (Siebke; R. T. Frank) and the disease is invariably cured by removal or irradiation of the ovaries.

(b) Fibromyomas have an incidence limited to the years of ovarian activity and diminish in size after the menopause, whether it be normal, surgical, or induced by radiation. Pathologic changes in the ovaries of patients with fibroids were reported by Seitz in 1911, and the cystic ovary as a contributory factor in their production has been claimed in a recent series of publications by Witherspoon.

From these pelvic neoplasms one can pass with some assurance that similar conditions will underlie analogous diseases developing in the breast.

III. CHRONIC MASTITIS

Chronic cystic mastitis is a term loosely employed by pathologists and clinicians for the diffuse neoplastic processes occurring in the human breast.
Under this head have been included various forms of epithelial proliferation, cyst formation, certain inflammatory processes, and diffuse fibrosis. For the animal experimenter, however, chronic mastitis has meant essentially epithelial hyperplasia.

A. Experimental and Pathologic Studies

Several investigators have reported the production of chronic cystic mastitis in laboratory animals by the continued injection of various hormones. One of the first of these attempts to reproduce a disease similar to Reclus' disease was reported in 1930 by Goormaghtigh and Amerlinck after the repeated injection of mice with follicular hormone. Wieser and Cramarossa have also studied the histogenesis of this disease by the injection of several hormones, especially the corpus luteum.

Many other workers (Lacassagne; Bonser; Burrows; Gardner et al), without drawing a strict analogy with the human disease, have reported atypical epithelial growth in the mammary glands of animals, especially of male mice, following the injection of various hormones, particularly those having an estrogenic effect. There is some evidence, furthermore, to show that this response may vary in different strains with a variable susceptibility to spontaneous tumor development (Gardner, Diddle, Allen and Strong; Lacassagne; Bonser).

From the simple morphologic study of human breast material from the various forms of chronic mastitis, evidence was early found to construct a theory that a hormone disturbance is an etiologic factor. One of the contributions preceding the modern research on the sex hormones was made by Moszkowicz in 1927. He was followed first by several Germans, more recently by a series of American writers, particularly Lewis and Geschickter. Cheatle stated that all the morphologic effects which he had observed in his own studies of Schimmelbusch's disease in women had been reproduced in mice, by Lacassagne, by the injection of the estrogenic hormone.

Great caution must be exercised, however, in applying to these conditions in animals the terminology used for the supposedly analogous disease in women, where fibrosis and cyst formation may be much more prominent than epithelial hyperplasia. The difference between the structure of the human mammary gland and, for example, that of the mouse makes it evident that similar pathological processes might result in morphologically different appearances. Nevertheless, a most important obstacle which must be overcome before chronic mastitis in women can be classed with the hormone-produced hyperplasias in rodents is the decided difference in the microscopic characteristics of the two conditions.

B. Clinical Studies

True clinical evidence of an ovarian dysfunction in women with breast disease must be sought first in the form of functional disturbances of menstruation and fertility, second in associated disease of the pelvic organs, and third by the use of the various biologic tests for the ovarian and pituitary hormones.
In a study carried out over the last five years at the Memorial Hospital, data of these three types have been collected on a group of 261 patients with so-called chronic mastitis. The detailed report of this work has been published (Taylor), and only a brief summary can be given here.

For the purpose of this study three types of diffuse breast disease were selected: (1) the so-called painful nodular breast; (2) the hypertrophied breast; (3) the breast with non-puerperal secretion. These were thought perhaps to represent contrasting forms of breast reaction to some specific constitutional states. The histologic characteristics of these conditions were studied, and the following major observations made.

(a) **Menstrual History:** The majority of women with chronic mastitis have a normal menstrual cycle, but there are many with a prolonged menstrual interval and a decrease in the amount of flow. This is especially true of the cases with abnormal secretion from the nipple.

(b) **Ovarian Pathology:** Records or personal observations of the ovaries of 68 patients with chronic mastitis who underwent an incidental gynecologic operation showed the great frequency of follicle cysts in the ovaries. The importance of this finding is open to question on account of the general frequency with which these cysts are observed.

(c) **Endometrium:** In 31 cases it was possible to study sections of the endometrium. These were important, since any general hormone disturbance affecting the breast should produce results also in the uterus. Of the 31 specimens of endometrium, all were found to be normal except three, in two of which a suggestion of glandular hyperplasia was present, and in one a carcinoma.

(d) **Excretion of Estrogenic Hormone:** The excretion of estrin in the urine was estimated, according to the method of Frank, for the entire menstrual cycle in 20 patients with breast disease. The average rates of excretion of the three types of chronic mastitis differed little from the normal controls or from each other.

(e) **Excretion of Gonadotropic Hormone:** Tests for the presence of prolan made by the Zondek and Katzman-Doisy methods showed no excess excretion.

(f) **Effects of Endocrine Therapy:** Irradiation of the ovaries resulted in a simultaneous diminution in the rate of the estrin excretion and in the severity of the breast symptoms. The administration of large quantities of estrin resulted in no increase in the severity of breast symptoms.

This clinical study of chronic mastitis indicates in the first place that an active ovary must be present for the disease to exist. Certain data including the high incidence of menstrual disorders and cystic ovaries point to an associated ovarian dysfunction in some cases. Analysis of the clinical histories, as well as the estimation of the estrin and prolan of the urine, has not to the present time proved that chronic cystic mastitis is due to any simple excess or lack of the estrogenic or gonadotropic hormone.

**IV. The Fibro-Adenoma**

The circumscribed tumors of the breast, notably the fibro-adenoma, are at first glance less suggestive of an endocrine lesion, since a hormone freely circulating in the blood stream should affect all parts of the breast equally.
A. Experimental Studies

Various experimental work has nevertheless demonstrated the responsiveness of the fibro-adenoma to hormone stimulation. It has been shown, for example, that benign mammary adenomas of rats undergo certain cellular changes during pregnancy (Emge and Wulff) and that lactation may occur even after their transplantation to the peritoneal cavity (Grauer and Robinson). Picco has reported sarcomatous changes in the epithelium of transplantable fibro-adenomas of the white rat after some months of folliculin injections.

B. Clinical Observations

Few clinical studies of patients with fibro-adenoma have been undertaken from an endocrine point of view. The disease of course does not occur before the puberty development of the breast, nor does one often, if ever, find a new fibro-adenoma beginning after the menopause. The ovarian function is therefore essential to the development of these tumors, although it is not necessarily the specific cause. There is some indication that fibro-adenoma has a predilection for women of special constitutional type, namely nulliparous women with relatively undeveloped pelvic organs and mammary glands (Taylor).

Evidences of a responsiveness of the already formed fibro-adenoma to hormone stimuli are easily found. Variations in the size of fibro-adenomas in women in relation to the menstrual cycle are well known, and microscopic changes have been reported (Ingleby). A more definite response is observed during pregnancy, when there is a marked hypertrophy of the epithelium to form the so-called lactating adenoma of the breast (Hunter; Kilgore; Krebzig). The occurrence of large quantities of estrogenic hormone in the tissue of a fibro-adenoma as reported by Geschickter, Lewis, and Hartman is of possible significance in their origin.

V. Carcinoma

A. Experimental Studies

The series of experiments which have demonstrated the relation of carcinoma of the mammary gland in mice to ovarian function has been an extremely important one, gradually developing over the course of the last twenty years. The work was initiated in 1916 by Lathrop and Loeb, who showed that in a tumor-bearing strain of mice the rate of tumor incidence could be lowered and the average age of onset raised by the prevention of breeding and by castration. This principle was amplified by Loeb in 1919 and corroborated by Cori in 1927.

A new step was taken in 1928, when Murray was able to produce mammary cancer in 15 of 210 male animals into whom ovaries had been transplanted at the age of from four to six weeks. The last stage has been the production of mammary cancer in male mice by the injection of various estrogenic substances. Lacassagne, working with a strain in which 72 per cent of the
females but none of the males developed spontaneous mammary cancer, obtained after weekly injections of estrin mammary cancer in all of the five males and in five of seven females so treated. With a strain in which mammary cancer occurred spontaneously in only 2 per cent of the females, he found that mammary tumors developed in two of eight males and in one of seven females. With still another strain no new growths developed among seven males treated in the same manner.

Confirmation of Lacassagne's work is gradually accumulating. The application by Burrows of ketohydroxyestrin twice weekly to the skin of 130 males resulted in two mammary carcinomas. Cramer and Horning have reported the development of mammary cancer in the glands of five males of a high-cancer strain following the painting of the skin twice weekly with an 0.01 per cent solution of estrin in chloroform. None of the females of this strain, however, developed a tumor after treatment with estrin lasting for more than six months. Still more recently Gardner and his co-workers have produced similar tumors in male mice by continued weekly injections of 500 international units of benzogynestrol.

Another logical line of investigation has been the study of the reproductive physiology of the strains of mice with a high incidence of mammary cancer. This work has concerned itself chiefly with an examination of the type of estrus cycle. Special characteristics in the duration of estrus or in the length of the cycles have not, however, been established for young mice of the strains with high tumor incidence (Bonser; Moskop, Burns, Suntzeff and Loeb). With the growth of the tumors, however, the cycles tend to become infrequent, with long continued periods of diestrus (Allen, Diddle, Strong, Burford and Gardner).

An important observation has been that the frequency of breeding has a great influence upon the incidence of spontaneous mammary tumors in mice. Thus a strain with a low cancer incidence among virgin females may be made to yield a larger percentage of mammary tumors by causing one pregnancy to follow another in rapid succession (Bagg). Whether the increased incidence in breeding mice is due to the continuous hormone stimulation of the pregnancies or to the irritation of stagnating products of secretion in the ducts is uncertain.

Finally, reports have indicated that hormones may be present in increased concentration in various mammary neoplasms. Extracts of mouse mammary carcinoma have been found to contain substances resembling the anterior pituitary hormone which accelerated the growth of young rats and caused premature opening of the vagina with estrus (Dobrovolskaia-Zavadskaia and Zéphiroff). An estrogenic substance was later isolated from spontaneous mammary mouse carcinoma by the same workers. Lacassagne has reported folliculin in colostrum, but Winter found only anterior pituitary hormone in the breast secretions of women during pregnancy or in association with various menstrual disturbances. Estrin has been detected in the tissues of a human fibro-adenoma (Geschickter, Lewis and Hartman). The finding of large quantities of estrogenic substance in normal human tissues, however, such as the psoas muscle, by Frank and his co-workers, reduces the significance of these observations.
B. Clinical Observations

In turning from experimental cancer to mammary carcinoma in women, many statistical observations are encountered which must be taken into consideration before the adoption of any theory of endocrine dysfunction as a causative factor.

(a) Age Incidence: In women about one third of the cases of breast cancer occur during the period of mature ovarian function, another third appear within five years before or after the menopause, while the remainder develop in older women whose ovarian function has ceased for five years or more. In the latter group at least, a direct relationship with ovarian function appears to be excluded.

(b) Child-bearing: Large series of statistics have repeatedly emphasized the fact that cancer of the breast is commoner in the unmarried and nulliparous woman than in the one who has had children (Lane-Claypon; Hoffman; Simons; Crile; Peller). This preference for the unmarried is in sharp contrast to the behaviour of mouse mammary carcinoma, where breeding has the effect of increasing the incidence.

(c) Lactation: The nursing histories of women with breast cancer have been the object of considerable study (Leaf; Lane-Claypon; Adair), and a theory has developed that the modern practice of shirking lactation is related to the increase of breast cancer. The contention rests on the belief that failure to nurse results in stasis and decomposition of secretions, which thus afford an irritating carcinogenic agent. Such a contention requires the pursuit of the investigation a step further to a consideration of the reasons for the nursing failures. In a personal investigation of the nursing histories of 349 children of women with breast carcinoma, it was found that 72 per cent were nursed for at least six months. Of the remainder, the great majority were not nursed because of an inadequate milk supply, and a negligible number were deliberately weaned by the mother. Nursing failure in the history of a patient with breast cancer may therefore be significant for two reasons. It may be evidence of the existence at one time of an inflammatory state from a stasis of secretions or it may be indicative of a physiological deficiency, possibly itself connected with an inherent predisposition to neoplastic growth.

(d) Menstrual Disturbance and Ovarian Dysfunction: As stated, a third of the cases of breast cancer develop within five years of the menopause, and these may theoretically be attributed to the irregularities of ovarian function common at that time of life. The cases of breast cancer developing many years after the menopause can, however, be connected with ovarian function only indirectly, through a theoretical development of malignant tumors from abnormal benign epithelial growths originating much earlier. Studies of the menstrual cycles of younger women with breast cancer have yielded no striking observations. Simons reported several cases of atypical menses but came to no definite conclusion as to their significance. Lane-Claypon also found little difference in the menses of women with cancer and a series of normal controls, but nevertheless clung to a belief in a relationship between tumor growth in the breast and menstruation. In a study made at the Memorial
Hospital of the menstrual patterns of patients with breast cancer, a point of possible significance was found in a change in the characteristics of the periods which frequently made its appearance shortly before the discovery of the tumor (Taylor).

(e) Anatomical Lesions in the Pelvis: The association of cancer of the breast with tumors of the pelvis is occasionally so striking as to suggest a general predisposition of the reproductive tract to the development of neoplasms. In this respect it is noteworthy that when carcinoma of the breast is associated with cancer of the uterus, it is usually with adenocarcinoma of the endometrium, another tissue subject to the ovarian function, and not with the squamous cancer of the cervix (Taylor).

(f) Effect of Hormones on Breast Carcinoma: In contrast to the meager evidence for an endocrine cause of human breast cancer, the effect of the ovarian hormone on already established carcinoma is more or less generally accepted. The extremely bad prognosis and rapid growth of cancer of the breast during pregnancy or lactation is one example. Another is the effect of removal of the ovaries. Bilateral oophorectomy as a method of treatment in recurrent breast cancer had a short vogue about thirty-five years ago (Bea-
song; Lett; Thompson; Cahen). The best results were apparently obtained, as was to be expected, when the operation was performed on women developing cancer before the menopause. The principle has been revised in recent years by the substitution of x-ray for surgical castration. By this method spectacular improvement is noted in exceptional cases (Hoffman), but its beneficial effect when applied to a series of patients may not be statistically apparent (Ahlbohm).

Summary

Any attempt to define the stage to which clinical and experimental work has carried the theory of an endocrine cause for breast cancer is difficult and is certain to receive little approval. The following points are nevertheless offered as perhaps the most important.

(1) The ovarian hormone is essential for the development and preservation of the epithelium of the mammary gland. Without it there is no tissue upon which any carcinogenic agent may act. This is the most obvious reason why cancer of the breast does not develop in early castrates or in untreated male mice.

(2) The development of breast cancer in mice after the injection of large quantities of estrogenic hormone may be brought about in several ways: (a) by a direct carcinogenic action comparable with that of various tar derivatives; (b) by increasing the normal physiologic impulse to proliferation until it produces atypical structures; (c) by the production of abnormal activities of the cells whose secretions provide the carcinogenic factor.

(3) Tumors of the human mammary gland are also dependent upon the ovary at least to the extent that the normal tissue from which the tumors must arise are provided by the ovarian hormone.

(4) An existent ovarian function is apparently essential for the common types of chronic mastitis and fibro-adenoma whose development is practically
limited to the years of mature sexual life. This is not true of carcinoma, which may appear long after the menopause.

(5) With the neoplastic disease once established, a marked response to variations in glandular function, such as those incident to pregnancy and the menopause, is noted in chronic mastitis and fibro-adenoma. A moderate reaction to these changes is observable in some cases of carcinoma.

(6) Some evidence of a glandular dysfunction can be found in certain cases of chronic mastitis, but hormone states comparable to those necessary to produce mammary carcinoma in mice by the injection of estrogenic hormone are unknown in women.

(7) There is no clinical evidence yet of any specific endocrine dysfunction as the cause of human breast cancer.

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