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Chronic cystic mastitis with special relation to carcinoma

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With

Special Relation to Carcinoma

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INTRODUCTION

The purpose of this paper is to better acquaint the student with the ever changing views of investigators regarding the relationship of Chronic cystic mastitis to carcinoma of the breast.

The author has borne in mind that until recent years very little work of an experimental nature has been done in this field. Consequently the material from which this paper is made up has been extracted from current articles upon this subject. He has set down clinical findings, experimental results, and theories of the different workers with an open mind. He has tried not to form an opinion but would rather let the reader form come to his own conclusions.

CHRONIC CYSTIC MASTITIS

Definition - Chronic Cystic Mastitis is a misnomer. Most authors agree that this disease can be divided into two separate varieties, one of which has been called Mazoplasia and the other Cystiphorous desquamative hyperplasia or cystic disease of the breast. The former is essentially a physiological process and is concerned with the hyperplasia of the epithelialium lining the ducts and acini of the breast and the desquamation of this lining. Clinically there is said to be pain over the whole of the breasts, often worse at menstruation. Women who suffer from this condition generally show evidence of ovarian hypofunction, their menstrual periods usually being of short duration and of scanty flow, and are, moreover, generally in poor health. In the latter the predominant feature is the formation of cysts. These are usually found in one of three ways; first as a single large cyst with the rest of the breast apparently normal; secondly, as a localized cystic change confined to one sector of the breast; and lastly, as multiple small cysts scattered throughout the breasts. (13).

The history of Chronic cystic mastitis dates back as early as 1831 when Sir Astley Cooper (12) in his work "On The Breast" distinguished one form of the disease, and described undoubted cysts belonging to this category. He reported a typical case occuring in a woman aged twenty-eight which became painful at the approach of menstruation. It was he who first described the blue tint typical of the unopened cyst, and recommended local removalor simple opening with a lancet and insertion of a piece of linen to bring about adhesive inflammation. (16).

Sir Benjamin C. Brodie (4) also described this condition in 1846 and mentioned the possibility of the cysts being multiple. He believed that the cysts were "originally formed by a dilitation of the lactiferous tubes". He was the first to report its restriction to the sexual period, saying, "I have never known the disease to occur previously to the age of puberty, nor after the middle period of life and if I am not much mistaken it is more common in single than in married women". However, he, as did Cooper, included cases of cysts complicated by papilloma. Brodie was the first to report a spontaneously disappearing tumor. He believed in expectant treatment with liniments in the cystic stage and

excision when firmer nodules developed. (16).

Valpeau (44) in 1856 described the condition as serous cysts of the breast. He recommended treatment by iodine injections in those cases in which the cysts exceded the size of a hazel nut. He compared them with hydrocele. The smaller cysts and those of solid tissue were treated with extripation. (16).

In 1883 Reclus (36) described the affection under the term "Cystic disease of the breast". He thought that the "multiple disseminated" and "bilateral affection of cystic production" distinguished the cases observed by his predecessors. Reclus called attention to cases of chronic cystic mastitis in which the disease appeared in the remaining half of one breast following previous removal of the other half. Also how following removal of one breast the other would frequently become involved. His microscopic description was more adequate than his predecessors. He quoted the histological studies made on his cases by Brissaud (6). The interstitial tissue was found healthy. The cysts were not thought to involve the lacteal conduits but the acini. Epithelial activity was noted in the acini

but no adequate description of hyperplasia was given. (16).

Schimmelbusch (39) in 1892 called attention to the same bilateral affection of the breast as described by Reclus, but emphasized the variety in which the cysts remained small and in which the diffuse "shotty" nodules had arisen from the epithelial hyperplasia in the acini. He called the condition Cystadenoma and stated that, "The pathological process consists of an increase of the acini in the single lobules which shows a great similarity to the proliferation which is found in the lactating breast ---Epithelial cells pile one upon the other and spread the diameter of the acinus --- Through this when the central lying epithelial cells collapse is the cyst formed. In forty-three cases he recorded that such patients who later developed Cancer (7%) showed this condition. Schimmelbusch stated, "It is, indeed, possible that cystadenoma may be placed in the category with certain epithelial conditions of irritation ---- which are in a sense benign but have a tendency to become malignant. He advocated bilateral mastectomy. (16).

In 1893 König (27) gave the disease the name of "Chronic Cystic Mastitis" and introlduced the inflammatory theory. (16).

From this review of older literature it can be seen that the blue-domed cyst typical in 60% of the cases of chronic cystic mastitis had been described. However, the essential distinction between the cystic and adenomatous form of the disease had not been made and the suggestion that the condition, while benign, might be precancerous served to throw the problem into a confusion that has persisted up to the present time. 1934 (16).

In 1921 Bloodgood (2) contributed the most extensive study and brought all the varieties of Chronic cystic mastitis together into eight subgroups based upon the size of the cysts and the presence or prominence of non-encapsulated adenomatous or cystadenomatous areas. Out of 271 cases of the cystic type he recorded 174 in which large cysts predominated, 28 cases in which diffuse cystic disease occurred and 61 cases in which there was diffuse cystic disease occurred and 61 cases in which there was diffuse dilitation of the ducts with or without small cysts; in 8 cases cysts were of the galactocele type. In the adenomatous groups he recorded 48 cases with non-encapsulated adenomstous areas, 18 with non-encapsulated cystic adenomatous

areas and 13 in which there was diffuse cystic adenomatous hyperplasia, described by himself in apre-vious report as senile parenchymatous hypertrophy. He came to the conclusion that chronic cystic mastitis was not as a whole, a precancerous lesion "but in the isolated and diffuse non-encapsulated cystic adenoma it may be safer to completely remove the breast or to perform the complete operation for cancer because of the incidence of cases in which cancer does occur, 2 out of 31 cases. (16).

Semb in 1928 and Cheatle and Cutler in 1931 separate the types of chronic cystic mastitis into these in which epithelial hyperplasia predominates and those in which a few large cysts dominate the clinical and microscopic picture. In their writings Bloodgood, Bemb, and Cheatleland Cutler have joined with Schimmelbusch in attributing the possibilities of malignant change to the adenomatous rather than the cystic type of the disease. Yet none of them have succeeded in untangling the apparent microscopical and clinical overlap between the two conditions. They also believe that the two types of chronic cystic mastitis essentially two phases of the same disease were capable of progressing into the other. (16).

Throughout this period of over one hundred years practically nothing of an experimental nature was contributed to substantiate the conclusions drawn from the clinical and pathological findings. In the last decade, however, the isolation of hormones from the placenta, from the ovarian follicle and corpus luteum, and from the pituitary, with the discovery of new methods of biological assay of these hormones has paved the way for the experimental interpretation of this disease. With the opening of this new approach to the problem there is definite promise of ultimately explaining the alterations in the structure of the breast and demonstrating the role played by physiological processes in the production of this disease. From the standpoint of these studies now in progress the pathological division of chronic cystic into a cystic type is related to the hormone of the ovarian follicle, while the proliferative type is under stimulation from the hormone secreted by the corpus luteum.(15)

PHYSIOLOGY

The breast has been studied from the viewpoint that it is not a resting organ but an organ having sex rhythm similar to the uterus and, therefore, pre-

senting different histologic pictures at different stages of the sex cycle. Sex hormones play an important role in the breast physiology and recent progress in the studies of these hormones has been a helpful aid in persuing knowledge of normal as well as abnormal breast function. (23).

The breast develops at prepuberty and puberty because of stimulation from the interstitial cells of the ovary. It attains full development and complete functional activity during pregnancy. The main factor in this development is the hormone from the corpus luteum which stimulates the epithelium of the breast acini and ducts. The corpus luteum in turn is under the direct influence of the hormone from the anterior pituitary gland. Con-comitant with the menstrual cycle the breast undergoes regular progressive and petrogressive changes. In the premenstrual phase under the influence of the corpus luteum secretion there is a rapid increase on the epithelial elements with production of outgrowths from the ducts and the following formation of new acini. In the postmenstrual phase there is a regression with disappearance of the newly formed small lobules, the

periacinar connective tissue shows a lymphocytic infiltration and the acini are filled with desquamating cells undergoing autolysis. These lymphocytes in the periacinar connective tissue gave rise to the early idea that this disease was inflammatory in nature, however, the lymphocytes are functional cells containing a lipase which is an aid inthe autolysis of the desquamating cells. (23).

The uterus shows failure of pregnancy by casting off its decidua in the menstrual flow, but the breast cannot get rid of its secretion and its desquamated epithelial cells except through absorption. This is due either because of the coagulation of the secretion, or keritinization of the cells or, it may be that the hypertrophy of the ductal epithelium obstructs the lumina of the ducts. It will be seen then that if the breast is to return to its resting phase there must be a complete balance between secretion and absorption, a condition which is under control of the internal secretion of the anterior pituitary gland and the ovary. (23).

If the luteal phase of the ovarian secretion is prolonged there will be an over stimulation of

the breast with consequent increased epithelization and hypersecretion. During the intermenstrual phase the breast will not be able to regress to the resting phase, and the result will be distention of the acini with desquamated cells and unabsorbed secretion. There will also be hyperplastic interacinar connective tissue infiltrated with lymphocytes. With the new luteal phase coming on with the next premenstrual period, more stimulation is applied and further distension of acini and ducts occurs. It is now evident why these breasts feel full and are swollen and painful. (23).

Cheatle and Cutler have named this disease "Mazoplasia" to show its functional origin and they would differentiate it from cystic disease of the breast, which they call cystiphorous desquamative epithelial hyperplasia. To them chronic cystic mastitis is a misleading term and should be discarded. Whitehouse agrees that the term should be discarded but contends that mazoplasia is a forerunner of cystic disease of the breast. Pickhardt, however, from his experiments on animals claims that chronic cystic mastitis can occur only if there is obstruction in the ducts, plus inflammation, plus a disordered hormonal secretion. (23).

Cystophorous desquamative hyperplasia presents a different pathology from that of mazoplasia. Histologically, epithelial changes are seen either in the ducts alone or more commonly in the ducts and acini. In the ducts the cells become elongated, feathery, and form colostrum-like corpuscles in certain areas. In the acini desquamation of epithelium occurs, the cells first of all becoming elongated and characteristically pale. These pale cells crowd in on the lumen, eventually disintegrate, and form small cysts, which, as the condition advances, coalesce with neighboring cysts to form larger and larger ones. Clinically this type presents itself in three ways: first, as a single large cyst with the rest of the breast apparently normal; secondly, as a localized cystic change confined to one sector of the breast; and, lastly, as multiple small cysts scattered throughout the breasts. These, then, are the two varieties--mazoplasia and cystiphorous desquamative hyperplasia--entirely separated from each other by Cheatle. (13). Experimental works on rats and mice show that injection of Theelin (folliculin, estrin, etc. early corpus luteum secretion), and theelin and progestin (progestin is late secretion of corpus luteum disappears

from urine just before menstruation following which involution occurs) in various ratios produces breast changes which simulates mazoplasia at different stages during the menstrual cycle in the human. "The age period at which chronic cystic mastitis is most common corresponds with the age period at which time these two hormones are most active." (28).

"The tendency of the cysts to vary in size and for the symptoms to be exaggerated in the premenstrual period is an expression of periodic variations of the secretory levels of theelin and progestin." (28).

Kilgore (1928) states that, "The chief common characteristic of all forms and stages of abnormal involution is an increase in the number of individual gland elements -- ducts or acini or both-- and the first stage in the process is one in which there is only increase in the number of gland elements. The lobules are full, contain many acini and are often packed closely together. Each duct or acinus, however, presents a fairly normal appearance under the microscope. There are described changes in the periacinal connective tissue in abnormal involution, but the size and contour

of the breast and the acini and the amount of epithelium at least remain practically unchanged. (26).

The theory is offered by d'Abreiu ( ) that mazoplasia, which is said to be a very common condition, may eventually in certain instances lead on to the cystic form of breast epithelial desquamation, and that all these breast changes are due to a faulty physiology. In other words, that all forms of nonmalignant nodularity, whether cystic or not, are due to a breakdown in the hyperplasia involution cycle occurring in the breast with each intermenstrual period and leading to a physiopathological process of excessive epithelization and cyst formation. The thyroid is an organ which, list the breast, undergoes cyclical changes from one menstrual period to another, and it may also, owing to a faulty physiology, undergo parenchymatous changes, leading to the formation of a goiter where there is an increased formation of acini. This stage may progress by involution carried too far or not far enough to the formation of nodular areas which may show increased acinar formation or increased colloid distension. So may the breast, then form a parenchymatous

nodularity which may progress to a cystic state. The cysts which are formed may show the characters of a hypo-involution with increased epithelial lining, or of a hyper-involution where there is one single layer of flattened epithelium. In other words, the breast may pass from the nodularity of mazoplasia to the cystic form of breast hypo-involution, and give rise, as in the thyroid, to a generalized or local cystic change or to one large cyst. (13).

Pichardt in his studies believed that patients suffering from this disease are "hyper" rather than "hypo". They are exceptionally active and alert rather than phlegmatic. He concludes then that there is hyperfunction of ovaries and shows this from Ancel's (49) experiments. Ancel states: "Corpus luteum induces a proliferation of the mammary gland." Pichardt's conclusion is further borne out by Loeb's statement; "The mammary gland under the stimulus of persisting corpus luteum secretion grows to a considerable size and resembles in character that obtained in pregnancy." (33).

He further states (Pichardt) that there are three elements necessary in development of chronic

cystic mastitis"(1) mechanical stasis; (2) inflammation; (3) proliferative elements due to some ephithelial growth stimulation, most logically a specific hormone of the corpus luteum, or graffain fallicle or both," (37) (35).

The definite tendency of both types of the disease to involve diffusely epithelial tissue of one or both breasts, to regress spontaneously, or to reappear or develop after excision, suggests a functional disorder, probably dependent upon the alteration in the character or amount of some hormone."(28)

Undeveloped tubules and acini in the adult breast ...may respond abnormally during the menstrual cycle and form the basis for the later development of cystic disease (mazoplasia) and adenosis. (Cystiphorous desquamative hyperplasia). Under the intense hormonal stimulation of pregnancy the lesions associated with chronic cystic mastitis frequently disappear. The eventual disappearance of the majority of all undeveloped tubules and acini after repeated pregnancies accounts for the fact that chronic cystic mastitis is rarely encountered in women who have borne many children. (28).

These findings also account for the frequent occurrence of cystic disease in married women who have not borne children and in the unmarried. The persistence of these structures through one or two pregnancies accounts for the disease in women who have borne few children. (28).

However, it has been shown by Cutler (1932) that "It is almost universally present in some degree until the menopause in normal breasts of all women who have borne children. The condition is also present during development and in the breasts of male and female infants at birth. It is present at puberty and pregnancy and during lactation. It is a physiologic rather than a pathologic process." (11).

SYMPTOMS

Cystic disease of the breast, which is more common than adenosis, is characterized by the appearance of one or more circumscribed, freely movable cysts of some size (1 to 3 cm. in diameter) which transilluminate well and may be associated with small, palpable nodules (minute cysts) in other parts of the breast. In one-third of the cases small nodules only, or dilated ducts, may be palpated beneath the nipple. The majority of the cysts appear in the mid-

zone of the breast. Pain, when present, is premenstrual. Discharge from the nipple rarely occurs, and, when it does, is serous or milky in character (colostrum). The breasts are usually of the virginal type, often with increased parenchyma and fatty tissue. The cysts remain freely movable and may disappear spontaneously. They are not found during child-bearing, but may persist beyond the menopause. (28).

In adenosis the mass which is palpable is usually smaller than in cystic disease. Multiple, indefinite nodules are usually palpable in both breasts. These are felt most distinctly at the periphery and give to the breast a definite edge. The more definite mass may be indurated and simulate a carcinoma by a tendency to infiltrate. The mass is rarely cystic. It is usually firmer, more irregular and may extend throughout a breast lobule. In rate instances the skin over such a mass is dimpled. The nipple may be retracted and blood may be discharged from the nipple (in 7 percent of these cases). The mass may be opaque when transilluminated. These lesions rarely persist during pregnancy, and tend to disappear with lactation and at the menopause.

The breasts, which are usually smaller than the average, may be unequal in size. (28).

Hawk and Brown (1937) feel that the commonest finding is diffuse lobular or nodular gland tissue, about 40 percent of cases. Of 64 cases, 86 percent had unilatoral symptoms but findings were bilateral in all but 28 cases. (22).

A so-called purulent discharge of the nipple was found to be associated with chronic cystic mastitis (cystiphorous desquamative epithelial hyperplasia) as well as with carcinoma according to Stowers (41); the discharge may be the first symptom. (22).

A localized collection of smally cysts occuring in a duct and its branches gives rise to a localized nodularity. Cutler states; "When the cystic state remains uncomplicated by papilloma and carcinoma, there is a tendency for one cyst to outgrow the others. A single cyst thus becomes palpable and dominates the clinical picture. An apparently single cyst rarely contains carcinoma. When papilloma and carinoma complicate the purely cystic state, there is not the same tendency for the development of a large cyst and the

clinical condition remains one of local nodularity. Thus local nodularity is a clinical sign of great importance because it usually signifies that the pathological process has extended beyond the purely cystic stage and that the condition is either localized Schimmelbusch disease or actually early carcinoma. (9).

Lewis and Geschicter found that the greater number of cysts were found in the mid-zone of the breast near the nipple or at the periphery. The cysts developed in the secondary system of ducts. These authors emphasize that there are two types of the disease. In one, cyst formation predominates the picture and they refer to it as cystic disease of the breast. The other is an epithelial hyperplasia predominating and called adenosis. They write that in adenosis the majority of the nodular areas are located at the periphery the characteristic saucer-like edge. They have, also, found that cystic disease is 5 times more common than adenosis and the majority have solitary large cysts predominating with associated small cysts. In this adenosis the nodules are usually smaller than cysts and

are more frequently bilateral and imparting a diffuse shotty feel with the saucer-like edge. There is a tendency to recurrence in 20 percent of the locally incised cases in both types. Milk may discharge from the nipple in 3 percent of the cyst cases and blood may discharge in 7 percent of the cases of adenosis. (22).

Pain was variously described by the patients of Rogers and Nathanson, as drawing, shooting, radiating, aching, fullness, tightness, and soreness, and varied in intensity from almost nothing to a severe pain which was a real disability. Out of 177 patients these investigators found that 70 percent showed definite relationship to catamenia and 30 percent a lack of relationship. (38). Practically all of these breasts showed gross lumpiness, either diffuse, localized or limited to a single lump, and ranging in degree from cases in which the breast felt like a bag of walnuts to those in which the gland tissue was palpable but within the probable limits of normality. (38).

Taylor, in his clinical studies, found the following statistics on the relationship of chronic cystic mastitis to the menstrual cycle: Of the patients

with painful breasts, 40.4 percent had abnormal menstruation (plus .1 percent which were cases of amenorrhea following hysterectomy); in patients having breast hypertrophy, 32.2 percent had abnormal menses and in these cases with secretion 59.6 percent had abnormal menstruation. Disturbances in cycle were the commonest in cases with discharge from the nipple and were usually delayed period or prolonged interval type. In disturbances of duration of menstrual flow the decrease in amount of the flow in cases of painful breasts was noted in 16.9 percent; this was also common in those with secretion from the nipple. Diminished menstruation cannot be accepted as necessarily a sign of ovarian under-function and may be dependent upon a local pelvic or uterine abnormality. Appearance of breast symptoms after hysterectomy was noted in 12 cases (271 studied), with either one or both ovaries retained. (42).

The two great types of abnormal involution usually present gross features permitting recognition at the operating table. The non-productive type (termed mazoplasia) presents one or many, large or small smoothed walled serous cysts with breast tissue present-

ing the usual mixture of fat and fibrous stroma of normal color and fairly normal elasticity. The productive type (so-called by Kilgore but termed either adenosis or cystophorus desquamative hyperplasia in this paper) presents single or multiple papillomatous cysts or a diffuse process of larger or smaller extent, with whitish-yellow necrotic material. The entire mass is typically harder and less elastic than normal breast tissue and often presents a distinct yellowish tinge on cut section. (26).

INCIDENCE

Lewis and Geschicter write that the disease occurs only in women, 3 percent being in negroes. They state that the majority of cases occur between the age of 35 and the menopause. The results of Taylor's work and clinical studies showed the average age of patients with pain to be 30.7 years, those with hypertrophy 29.1 years and those with secretion 35.6 years. (22).

However, Hellwig does not agree with this. He performed 121 operations on the mammary glands, in which 63 had a chronic cystic mastitis. Thirty five cases concerned a simple chronic cystic mastitis (mazoplasia), 2 cases a chronic cystic mastitis with marked epithelial proliferation (cystophorous des-

quamative hyperplasia), 3 cases a chronic cystic mastitis with a typical epithelial proliferation and 20 cases a chronic cystic mastitis with carcinoma. While the average age for the simple cases was 38, it was 40, 45 and 52 years,respectively, for the other three types. Of the cases of the first type, 32 concerned women, of which 27 were married. The three remaining cases of the first type concerned men. (20).

Lewis and Geschicter further state that the majority of cases of both types of disease occur in married women who have not borne children or in unmarried women. Cystic disease tends to disappear during the first half of pregnancy and adenosis rarely persists through pregnancy with tendency to disappear during lactation. Cystic disease occurs in married women on an average of 10 years after nursing the last child. The mass in adenosis may be opaque to transillumination. The breasts in this latter type are usually smaller than average and may be unequal in size. Bloodgood noted that chronic cystic mastitis,especially the adenosis type, was never seen in fat women. (22).

PATHOLOGY

The 500 cases which formed the material for d'Abreiu's investigation ranged from the ages of 10 to 80 and were divided into age groups of 10-20, 20-30, 30-40, 40-50, and 50 upwards. Nodularity of the breast in greater or less degree, and showing all the clinical signs indicative of mazoplasia, was found in 144 cases --- a percentage of 28.8. Of these 144 cases, 66 were single and 78 married. (Of the latter 78, 40 had suckled one or more of their children). The percentage incidence of nodularity in the various groups was as follows:

10-20	28.6
20-30	33.0
30-40	32.0
40-50	33.0
50 upwards	21.0

These figures show in a striking manner the universality of the nodular breast. It is, roughly speaking, equally common in the married and unmarried, and the three decades between 20 and 50 show a remarkable equality in the incidence of the condition -- namely, 33, 32 and 33 percent. (13).

Nearly all of those who were between puberty and the menopause showed signs of ovarian hypofunction, their periods being painful and scanty, and were of the asthenic, chronically, unhealthy type.

Before puberty it does not occur, and after the menopause an involutionary cure is brought about. Of the 500 cases examined, only 46 complained of pain in the breast, and of these 46, 20 (nearly half) had no signs of mazoplasia or cystic change whatever. Moreover, in the 26 who had nodular breasts which were painful, it was found that the pain bore no relation to the degree of nodularity found. (13).

By far the majority of nodular breasts--98 out of 144 (68 percent) made no complaint whatever of pain, and the conclusion became obvious that pain was not a feature of the condition. (13).

That the definitely cystiphorous stage is relatively uncommon was shown by the fact that only 20 out of the 500 had demonstrable cysts in their breasts. (13).

There were 33 cases of carcinoma of the greast in the series: of these, 6 showed nodularity or cystic change elsewhere in one or other breast, giving a percentage of 18. It is, of course, possible, however, that the nodularity in these cases was secondary to the malignant growth. (13).

The average age of patients with non-cystic nodular breasts was 36, in those with cysts it was 40, and in the malignant cases 50. (13).

Lewis and Geschicter (1934) have analyzed the clinical findings in 600 cases of chronic cystic mastitis. Cysts may persist in isolated instances after the menopause, but adenosis tends to disappear at that time. Secondary tubules and lobule formation with the development of potential acini do not occur until adolescence. The secondary ducts, which are the seat of cystic disease, and the acinar elements of lobules, changes in which give rise to adenosis, are, therefore, not present before puberty. Physiologically, actively functioning ovarian tissue is not as a rule present after the menopause, and the ovarian hormones, which undoubtedly exert a great influence on breast tissue, are no longer active. (28).

The changes in cystic disease and adenosis may be contrasted as follows: Cystic disease affects the preformed structures, the ducts and tubules; whereas adenosis affects the terminal ends of the tubules from which develop new acinar elements. Cystic disease is essentially a ripening process by which the thickness

of the adult epithelium of the ducts is increased. This is followed by liquefaction and desquamation, resulting in dilatation of the duct system and canalization of the epithelium. Adenosis is essentially a proliferative process by which a number of new and incompletely differentiated elements are laid down in the region of the terminal tubules (acinar zone). This fundamental pathological distinction between maturation and proliferation corresponds to the two distinct effects of the two ovarian hormones. (28).

Handley, although a dissenter inthe view that the etiological factor in chronic cystic mastitis is abnormal involution, describes the pathological process as follows: "When an area of chronic mastitis is examined great variations are found in the appearence of closely adjacent lobules. It must ...be admitted on general principles of interpretation that these varying appearances represent different stages of the same process. The earliest stage will be seen in lobules, if such can be found, which show no hyperplasia, either of the connective tissue or of the epithelium. If other lobules show great connective tissue hyperplasia without epithelial change it will have to be inferred that connective

tissue hyperplasia precedes and probably causes epithelial hyperplasia. If,on the contrary, many lobules show advanced epithelial proliferation without surrounding connective tissue changes, then one must accept Cheatle's view that epithelial hyperplasia is the primary change. Connective tissue hyperplasia clearly precedes epithelial hyperplasia, for lobules showing normal connective tissue with proliferated epithelium cannot be found." (18).

"In an area of chronic mastitis those lobules which show practically normal acini with no evidence of abnormal epithelial activity are in a state of lumphatic congestion with distension of the lymph vessels and spaces. On the other hand, those lobules which show precancerous epithelial change show in addition the working of a fibrotic process which has much increased the total intralobular fibrous tissue and has obliterated the intralobular lymph vessels and spaces and destroyed the perilobular lymph sinus." (18).

"Still more briefly it may be stated that in early chronic mastitis there is lymphatic stasis,

in late chronic mastitis lymphatic obliteration with the formation of new fibrous tissue. As Victor Bonney has shown, the new fibrous tissue differs from the normal fibrous tissue in not containing elastic fibres." (18).

Microscopically, the outstanding features of cystic disease are:

1. The formation of large and small cysts with or without an epithelial lining.

2. An increase in the entire duct system associated with dilatation of the secondary and terminal tubules.

3. An increase in the epithelium lining the duct system.

4. A tendency for this epithelium to approach the differentiated columnar type and then liquefy or desquamate.

The epithelium is always of the adult type, and the pathological process is one of maturation and is an hypertrophy. Wherever epithelial changes occur there is apparently a concomitant attempt at lumen formation. (28).

The salient features of the microscopic pathology of adenosis are:

1. An epithelial proliferation in the terminal tubules of the lobules which give rise to small, multiple adenomas and papillomas in the tubules.

2. An increase in the acinar elements, the acinar epithelium proliferating and invading the surrounding fibrous tissue.

3. Dilatation of the tubule or acinus distal to the point of obstruction by adenomas or papillomas. (28).

One of the striking features is the small, oval cells with prominent nuclei found at the periphery of the lobule. The newly formed acinar elements are not well differentiated and frequently have no lumen. New elements are formed as the result of proliferative activity and the process is a hyperplasia. (28).

d'Abreu in his investigation of a series of sections of breasts of female post-mortem cases with no history of breast disease when examined, the following conclusions were arrived at:

1. Mazoplasia--It was expected in view of the clinical frequency of nodular breasts that mazoplasia would be seen in a large percentage of these

sections. The histological picture of the condition was actually found in almost every instance (15 out of 17) whether cysts were also present or not.

2. Cysts--If mazoplasia, a very common condition, is the first stage of a process leading to clinically obvious cyst formation, then an intermediate stage where cysts are demonstrable microscopically only would be found with a frequency less than that of mazoplasia but greater than that of clinical cystic disease, and this in effect was what these sections showed. Out of 18, 8 showed cysts larger than that of the average glomerulus. Moreover, in these sections there were always to be found areas of mazoplasia, and all stages of cyst formation from the slight terminal distension of ducts and acini seen in the latter, to those visible to the naked eye, and showing all the characteristic cytology of cystiphorous desquamative hyperplasia. In short, the difference between mazoplasia and the cystic breast seemed to be in degree and not in kind (13).

Histologically some cysts are true retention

cysts with no evidence of epithelial hyperplasia. These are to be explained as a localized area of hyper-involution. In two cases papilliform projections into cysts were seen. These epithelial proliferations were hyperplastic and not neoplastic, the cells being equal and typical. (13).

A series of sections of portions of cystic breasts removed surgically were examined, and in some cases the benign neoplasia seen in the walls of cysts where cellular activity was greatest showed a different picture. The connective-tissue element of the papillae had decreased, and cell masses were formed. The cells were not irregular and atypical, but the possibility of such a condition being precancerous cannot be ignored; the postmortem cases, however, show that unsuspected cysts are so frequent that the cystic state cannot be generally condemned. Cases should be treated as premalignant only when microscopical section following biopsy reveals the picture just described. (13).

Of greatest importance is the relationship between cystic breast and mammary cancer. All authors agree that carcinoma can arise from this condition,

but they differ in the frequency with which such a change can take place. Most authors give figures of 30 to 40 percent. Borchardt has endeavored to show that the percentage is much smaller. He quotes the significant statement of Hellwig: "That in 90 percent of cases, amputation of the breast in cystic mastitis is a useless mutilation." (3).

Borchardt and Jaffe investigated both breasts of 100 women over forty years old. Stained sections were examined microscopically, 90 percent of the series showed cystic formations in one breast; 70 percent showed cystic formations in both breasts. These cystic changes in breasts apparently normal and healthy, differ very little from the changes characteristic of cystic mastitis. If these cysts are precancerous, then 65 percent of all women over forty have a precancerous condition of one breast, and thirty percent of both breasts. (3).

Cutler would place the incidence of cancer following chronic cystic mastitis at a higher percentage. He states that, "About 20 percent of all carcinomata of the breast can be definitely stated to begin within the lesions of the cystic state. Beginning as an epithelial hyperplasia the process

may end in the cystic state. If the process continues papillomata form within the cysts and Schimmelbusch's disease is the result. The process may stop at this stage, but if it continues carcinoma is the inevitable consequence. The proportion of cases in which cystic disease and Schimmelbusch's disease end in carcinoma is impossible to estimate. We do know that full 20 percent of all carcinomata show evidence of having passed through these various stages." (9).

The epithelium in the microscopic cysts is active and is more likely to become neoplastic than the degenerated epithelium that lines the larger cysts. Once a cyst has become large, it can be considered, with certain rare exceptions, as immune to neoplastic change. The development of papilloma and carcinoma occurs, therefore, as a rule, in the small microscopic cysts and not in the large ones. (11).

When the papillomatous process complicates the cystic state the area of distribution occupied by the papillomas is in the same ducts and acini which are affected by the cystic state and in them only. The change from the cystic to the papillomatous state can be seen in all stages of transformation. Cystic disease of the breast begins in

the late twenty and early thirty years of life. Papillomas make their appearance most commonly in the late thirty and early forty years of life. (11).

The consequences of cyst formation are stagnation of contents and the supervention of a neoplastic process (papilloma, Carcinoma). On the formation of a cyst there is stagnation of its contents, and it is conceivable that among these contents may be irritants that continue their action undisturbed over long periods. The fact that benign and malignant tumors do not always occur in situations in which there is stagnation plainly indicates that there must be other factors in addition to stagnation. (11).

It is impossible to determine the prognosis of small microscopic cysts. Carcinoma arises by this method in 20 percent of all cases of carcinoma of the breast. The percentage of cases of cystic disease that eventually end in carcinoma is at present impossible to determine. In estimating the prognosis of cystic breasts it is important to consider numerous facts:

1. When cystic disease progresses it passes

into the neoplastic state (papillomas), and this state in turn may pass into the carcinomatous state.

2. There is no clinical evidence to indicate these transitions.

3. The sequence of events may cease at any point.

4. When carcinoma develops it generally appears twenty-five or thirty years after the incidence of the cystic stage. (11).

Cheatle has called attention to the following important sequence. Cystic disease begins in the late twenty and early thirty years of life. Papillomas make their appearance in the lesion during the late thirty and early forty years of life, and carcinoma appears in the lesion in the late forty and early fifty years of life. (11).

d'Abreu believes that all cysts are due to faulty involution; frequently they are found to have the appearance of a true retention cyst, the lining consisting of one flattened layer of cells with no evidence of cellular proliferation anywhere. These are to be regarded as areas of hyper-involution. Cysts with an epithelial lining are the result of an incomplete involution. The next stage from cystic formation is the supervention of

epithelium is not degenerated so extensively. This epithelial neoplasia is at first benign and appears as a papilliferous outgrowth into the lumen. Later still these epithelial outgrowths may become sessile and lose their connective-tissue element; the cells are de-differentiated and the picture beings to take on the characters of malignancy. (13).

The facts that the fluid in cysts contains irritant substances such as urea, that experimental tar carcinomata of the breast in rodents show the stages of preliminary desquamation, and that there is evidence that cellular growth is stimulated by autolysis of cells apart from any irritant substances produced by such autolysis, are reasons for believing that cystic changes in the breast may lead, in certain cases, to malignancy. (13).

Rodman believes that chronic cystic mastitis is not definitely precancerous, however, carcinoma does occur in a low percentage of cases. In a later paper (1935) he states that "chronic cystic mastitis is associated with carcinoma in from 15 to 20 percent of cases (15.5 percent in his own series). (35) (37).

Dr. Lacassagne in his experiments on male mice in which he injected estrin found that carcinoma developed in all cases if estrin injection was prolonged. Cheatle in his review of Dr. Lacassagne's work, states that the pathological transition undergone by these breasts is identical with Schimmelbusch's disease in the human. He further contends that Schimmelbusch's disease is in no way related to mazoplasia. He says, "It will be fairly obvious that the changes in the newly-formed breast tissue are the same kind and sequence as in Schimmelbusch's disease. It also appears obvious that the changes leading to carcinoma do not occur in the normal immature breasts of the mice, but that they appear in the new and abnormal tissue.... The sections support my contention that Schimmelbusch's disease is unrelated to mazoplasia, of which there is not the slightest sign. They also support my belief that cystic breasts in Schimmelbusch's disease should be removed." (8).

In relation to estrin therapy in mazoplasia and its probability of acting as a causative agent in cancer, Cheatle feels that it is not dan-

gerous. He states, "In considering this point, it must be remembered that every pregnant woman and mare is flooded with estrin with no bad effect."

"In all my sections I cannot discover an indication that mazoplasia is related to carcinoma."(8)

Campbell in analysis of literature and 290 cases of his own series states that cystic disease is not a precancerous lesion and malignant changes are no more likely to develop in cystic breasts than in normal breasts. In treatment complete removal of breast removes all worry of carcinoma but from functional and cosmetic standpoint conservatism should be used and local excision of lump can be done. All single solid tumors in women over 25 years should be removed for diagnosis, when the cysts are multiple the risk involved does not warrant an extensive procedure or loss of the breast. (7).

TREATMENT

"The treatment of this obstinate complaint presents a difficult problem. The chief reason for the difficulty is that the condition is a local expression of a systemic dyscrasia." (9).

"Local treatment has little beneficial effect. Diathermy and x-ray therapy may effect temporary improvement but in general these agents have proved of little value. Women suffering from painful breasts caused by this condition commonly show evidence of ovarian hypofunction. The menstrual periods are frequently of short duration and the flow is usually scanty. Administration of ovarian residue has resulted in the relief of pain in many cases of this type." (9).

In reviewing this subject it may be seen that, in the past, based on the conception that chronic cystic mastitis was a cancerous or precancerous lesion, the treatment holding first place was radical surgery. With the recent advances in the understanding of the disease and the advent of endocrine therapy, new possibilities in treatment have arisen. (22).

The two methods of treatment now used are endocrine therapy and surgery.

In endocrine therapy the two products used by Rogers and Nathanson in their cancer clinic, are ovarian residue (Wilson) and an oral preparation of

Progynon (Schering). Ovarian residue is the extract of the whole ovarian substance minus the corpus luteum hormone--progestin; Progynon is the follicular hormone--estrin. Dosages used were: Ovarian residue 1 capsule (5 grs.) t.i.d., or Progynon 1 tablet (45 Allen-Doisy rat units) t.i.d. (22).

Although the method described used the oral route for medication, more potent concentration of the estrin preparation may be assured by intramuscular hypodermic injections.

Whitehouse feels that theelin has great therapeutic values in chronic cystic mastitis; Cutler used ovarian residue with good results. (22).

Dahl-Iverson treated 22 cases with estrin. 18 of these cases showed considerable recovery, 2 had aggravation of symptoms, (they were between ages of 20 - 30), and 2 had no effect. Estrin is contraindicated just before the menopause as there is already an excess of estrin present in the blood stream. (14).

The dosage is 2000-4000 mouse units daily by mouth and supplemented by 10,000 - 20,000 mouse

units, intragluteally once a week. The course of this treatment is from 3 - 6 months.

Remedy by this treatment is more than symptomatic as has been shown biopsy following treatment. During this regime of treatment the breast should receive support but in no way be compressed. Surgery is inadvisable unless estrin is to no avail. (14).

"Rational surgery of cystic disease of the breast follows logically from the pathology and the tendency to cancer discussed. For isolated areas of the nonproductive type of abnormal involution, mazoplasia including the single blue-domed cyst, the establishment of diagnosis by exploration and the removal of the lesion and a small zone of surrounding breast is sufficient. Conservation of the remaining breast is entirely justified. The breast is not more likely to develop cancer than is normal breast. There are only two reasons for removing the whole breast; (1) the possibility of small cysts in remaining breast tissue later developing into large cysts, i.e., recurrence requiring the annoyance of another operation; and (2) the possibility

that if cancer should develop the patient might fail to observe it in the presence of an otherwise 'lumpy' breast. Certainly neither of these reasons is an absolute one."(26).

"In the productive type, adenosis, on the other hand, it is essential that all the tissue affected by the process be removed--local removal of an entire localized area--removal of the entire breast or of both breasts if the process be diffuse and general. Furthermore the physical characteristics of cystadenoma make it one of the most difficult of benign lesions to differentiate from cancer at exploration." (26).

"Since the process frequently involves a considerable amount of breast and frozen sections of one or a few scattered areas cannot be safely trusted to rule out cancer, and since experience shows that cancer is already present at the time of first operation in a considerable number of cases, the surgeon must be prepared to do an occasional radical operation when the pathology is in doubt." (26).

In the group of 121 cases studied by Hellwig (1930) induration was present on the average, sensitiveness to pain was uncommon and pain was rare 1-1/2 years before the patient came for an operation. The cases of type two were characterized by marked epithelial proliferation leading to the true papillary form. One-third of all the women over 40 years of age were in the initial stages of chronic cystic mastitis. In half of all the cases of mammary carcinoma no changes in the sense of a chronic cystic mastitis were demonstrated. Half of the cases of chronic cystic mastitis were diagnosed clinically as malignant. The other half was correctly diagnosed microscopically, usually with Wilson's method during the operation. A bleeding mammary gland was not considered as an indication, for, according to the writer, this constitutes an uncertain symptom. Removal of the gland is an unnecessary mutilation in at least 90 percent of the cases. It was totally extirpated owing to histological evidence of threatening malignancy in only 3 out of 40 cases of uncertain carcinoma. Since the writer believes that one may determine during the operation whether or not there is a

tendency to malignancy, he rejects amputation in the so-called benign cases. (20).

"Although the exact mechanism remains to be determined, it now appears certain that an important relationship exists between the benign breast changes and the endocrine system....If for practical purposes one may assume that in cases which respond to appropriate endocrine therapy there remains no question of premalignancy and hence no need for operation on prolonged observation, then we have a valuable diagnostic agent whose use would greatly simplify the management of benign breast conditions. At present one feels justified in acting on this assumption only that is when the breast tissue returns to its normal consistency as a result of medication." (38).

"Medication was given only the ten days preceding the onset of each menstrual period for a period of three months. Each patient would return after three months for an examination. If both subjective and objective symptoms were found to be completely relieved, the treatment was discontinued and case closed. If the result was in

8 of these there was complete relief of breast symptoms and disappearance of lumps."(38).

As well as being of therapeutic value, the use of this treatment is also of diagnostic aid, as was before stated. Drs. Rogers & Nathanson state: "One is assuming that complete disappearance of lumps from the breast warrants the belief that no precancerous lesion is present... A partial or total failure to respond to medication, however, cannot be taken as indicative of a precancerous lesion, but neither does it indicate its absence--what advise to give the patients remaining in this group is difficult, and will be a problem until the pathologists agree on what constitutes a precancerous lesion of the breast. (38).

From Dr. Lacassagne's work on mice, Cheatle feels that it would be unwise to administer ovarian residue in women suffering from cystic breasts. (8).

It appears that Rodman's method of handling these cases is as good as any. In papillary cystoadenomata, representing as they do a further increase in epithelial activity in women over 35 years old, a simple amputation of the gland is best. In chronic

conclusive another three months trial was started, using the other product. If this also failed, medication was discontinued and operation advised.

Out of a group of 32 patients, Drs. Rogers and Nathanson, 19 cases which were unmistakably improved. This number compared to the relatively small number of patients in the control group showing spontaneous recovery is significant. "Ten of the treated patients had been followed from one to four years before treatment, returning regularly because of presence of symptoms. Of this particular group to date, 6 have shown complete relief, one partial relief, and one an exacerbation of symptoms coincident with treatment." (38).

"The majority of patients who were improved did not show relief until after a period of a month or more of treatment. Some, however, described prompt effects. (38).

Out of 20 patients with symptoms associated with menses, 14 described periods as scanty, 1 scanty and irregular, 1 irregular, 4 normal. "Following treatment 8 reported periods more regular, more profuse, and more prolonged, and in all

cystic mastitis, cases are divided into women under 35 and those beyond 35. If under 35 and the lump or lumps do not change appreciably for at least two months during the menstrual phases, then the lump should be removed for microscopic study; if benign, that will suffice. If over 35 and the lumps do not change appreciably after two months observation, simple amputation is best done. A well trained pathologist should be on hand to make frozen sections of the most suspicious areas, the pathological diagnosis serving as a guide as to how radical the amputation should be. (35).

"Semb made this interesting observation in 6 of 78 cases: "cystic mastitis, without cancer was present in one breast, while cancer without cystic disease was present in the other." (40).

Realizing that there is a tendency for cancer in women past 50 suffering from a gross cystic disease, the author recommends radical operation in such cases, i.e. amputation of the breast and removal of the axillary glands. The operation is not complicated by removing the latter, at the same time precluding the possibility of overlooking cancerous foci. In other words, operation means for a

certain proportion of women an early operation for cancer; for others, it is prophylaxis against cancer of the breast. Of course, not all of these women would eventually have cancer. It has been asserted that 50 to 60 percent of patients submitted to operation because of fear. (3).

Conservative therapy must be recommended for the mastopathies of young women whose complaints are slight and who show very little on examination. They require no surgical treatment for they are not endangered by cancer. Even with manifest pathology they can be treated conservatively. Very often simple puncture of the cysts results in permanent cures. (3).

Elmer W. Smith stated that his conception of a chronic cystic mastitis was that of the smaller, multiple, dilated acini that is encountered in regions of proliferating interstitial fibrous tissue, which shows marked collections of lymphocytes. Cysts so produced, he believes, never reach the proportions of the single blue-domed cyst or cyst adenoma of Dr. Kilgore's nonproductive type. (46).

Dr. James F. Percy feels that the dangers of postponement necessitated by proper laboratory

study can be greatly minimized and probably entirely overcome if, when practicable, "two things are done as the most essential part of the biopsy technic. First, that the involved tissues be removed only with the cautery. And second, that all of the visible and palpable structures in the pathologic process be removed. This, from my point of view, is the only perfect and complete biopsy, and when combined with an immediate frozen section, permits of the most reliable determination of the character of the pathology in the breast, especially when passed upon by a trained and experienced pathologist." (48).

Dr. Edwin I.Bartlett feels that, "A surgeon is no longer justified in operating on any breast without a knowledge that will enable him to interpret what he sees at exploratory operation or without a pathologist with that information to advise him. Furthermore the time has come when hospital pathologists must be thoroughly trained in breast-gland histology because the number of breasts to be explored is already considerable and is increasing rapidly. Careful study of this and other articles is highly recommended and, above all, thorough study

of all breast specimens, both at the operating table nad later in the laboratory." (47).

CONCLUSIONS

1. Mazoplasia and Cystophorous disquamative hyperplasia is brought about by abnormal involution of the mammary gland.

2. Mazoplasia is definitely not a precurser of carcinoma. Treatment is best obtained by endocrine therapy.

3. Cystophorous desquamative hyperplasia is a precancerous lesion and should be treated accordingly. This is best done by breast amputation.

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