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Relation of chronic cystic mastitis to carcinoma

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HISTORY

The first reference to chronic cystic mastitis to be found in literature was made by Sir Astley Cooper (1) in 1845. At that time, he described a typical case of a young women, age 28, with a nodular breast and premenstrual pain. In discussing the subject he described the appearance of a blue-domed cyst and recognized the co-existance of chronic cystic mastitis with cancer.

One year later, 1846, Sir Benjamin C. Brodie (2) described the blue-domed cysts in more detail and mentioned the fact that the cysts may possibly be multiple, and that the disease was benign in character.

Warren (3) in reviewing the history describes the work of Reclus, Schimmelbusch, Koenig and Tietze. Reclus, in 1883, further carried on the investigations of his predecessors. He described the main features of the disease as the multiplicity of cysts, and simultaneous bilateral envolvement, and discovered that chronic cystic mastitis was a frequent rather than rare disease. Schimmelbusch, in 1892, believed the condition was truly malignant, and found cancer developing in 3 cases out of 43 he was following. He gave the name "cystadenoma mammae" to the disease and stated that it had a tendency to become malignant. However, it must be stated that Schimmelbusch included papillomata and epithelial pro-

liferation in a new hyperplastic state as being a part of the same disease. Koenig, in 1893, introduced the present name of the disease, chronic cystic mastitis, on the basis of round cell infiltration and an inflammatory appearing condition. Tietze, in 1900, pointed out the epithelial proliferation within the cysts and noted a 10% incidence of carcinoma in chronic cystic disease. Warren (4) noted the epithelial changes of Tietze and termed it "adenomatous proliferation". He found that this condition coexisted with carcinoma of the breast in 15 of 507 cases.

Bloodgood (5), in 1906, believed that senile "porenchymatous hypertrophy", as he called it, was a precancerous lesion in as high as 50% of cases. However, he completely reversed this opinion in 1921 (6). In a series of 350 cases, Bloodgood had opportunity to study gross and microscopic sections of 222 cases and could find no evidence of carcinoma.

Greenough and Simmons (7), in 1914, believed an incidence of carcinoma occurred in 4.8% of cases of chronic cystic mastitis with a 1 to 17 year follow-up after local excision of the palpable lesion. Deaver and McFarland (8), in 1917, thought the disease to be abnormal involution and further thought that the adenocystic state

developed carcinoma in 10% of cases. Ewing (9), in 1919, found minimal carcinomas in 50% of breasts excised for cystic disease.

Cheatle and Cutler (10), in 1930, studied the disease extensively in an attempt to classify it as to origin, gross and microscopic picture, and its relation to carcinoma. It was their opinion that chronic cystic mastitis in its third stage, "malignant epithelial neoplasia", was responsible for 20% of all carcinomas of the breast.

Lewis and Geschickter (11), in 1934, studied a group of 271 cases with "adenosis" for more than 5 years and found 3 died of breast cancer. In another group of 252 cases of cystic disease only 1 died of breast cancer (12). They therefore, concluded the disease was benign. Campbell (13) continued research along the same lines as Lewis and Geschickter, and by a study of a series of 290 cases concluded the disease was benign.

Warren (4), in 1940, studied the situation extensively. He computed the attack rate of female population of Massachusetts by cancer. He then did the same for those with chronic cystic mastitis. Also included was a control group in Toronto, Canada. His conclusion was that carcinoma of the breast develops 4.5 times as

often in women with chronic cystic mastitis as in the average female population. It must be stated, however, that Warren included fibro-adenomas and intracystic papillomas.

Logie (14), in 1942, examined 330 consecutive cases of breast tissue. Of 118 with carcinoma, 67 showed mastopathia cystica. It is Logie's opinion that mere chance could not account for so high a percentage of carcinoma, and he concluded, therefore, that a definite relation exists between chronic cystic mastitis and carcinoma of the breast. Vonden Berg (16), in 1943, on the other hand, followed 57 cases for an average of 7.2 years and found only one malignancy arising during this time.

Geschickter (15), in 1943, on analyzing 793 cases and following them over a period averaging 10.2 years, found that women affected by cystic mastitis were more predisposed to carcinoma than women unaffected by this disease. His estimated percentage of predisposition is somewhat lower than that of some previous investigators, it being twice as much in cystic disease, 5 times as great in adenosis, and zero in mastodynia, this last of which he includes as a portion of the disease.

Reed (17), in 1948, followed 26 cases from 11-17 years, but found not a single carcinoma developing. The

original site of disease was excised. Tice, Dockerty, and Harrington (18), in 1948, believed, as did Reed, that the lesion showed no relation to carcinoma of the breast. However, Coppleson (19) was of the opinion that duct popilloma and cystic mastitis are precancerous.

ETIOLOGY

Etiology of chronic cystic mastitis is in a confusing state. There is no uniformity of opinion as to the exact origin. If this could be arrived at successfully, it would undoubtedly aid in answering the main question of this thesis.

Sir Benjamin Brodie (2) voiced an opinion in 1846 that the cysts were formed by dilitation of the lactiferous tubular. Schimmelbusch (3) stated that the process consisted of an increase of acini in the single lobules similar to that found in the lactating breast. Epithelial cells piling one on the other with cells toward the center of the acini, degenerating, sloughing into the acini, and dilating them. Thus cysts are formed. Reclus (3) agreed with the work of Schimmelbusch, and states that: "cysts are formed by secondary degeneration in areas which have undergone epithelial proliferation."

McFarland and Deaver (8), from 1917 to 1922, described the disease as originating from senile or presenile involution. Intracystic popillomata was described as being a remnant of broken-down lobular septae. These men also were among the first to describe local variations of breast, due to hormonal stimulation. Cheatle and Cutler (10), in 1931, advanced the hormone theory of cyst formation of McFarland and Deaver. It was Cheatle and Cutler's belief that the ducts are the prime source of the cysts, and that dilitation of the ducts is due to the passive distention of the ducts by fluid secreted from the periphery of the ducts. Epithelial proliferation being the most prominent feature. Epithelial cells desquamate into the lumen further distending the ducts.

Taylor (20), in 1936, theorized that the etiology lies in hormonal imbalance. He cited 82 cases in which simultaneously chronic cystic mastitis and menstrual irregularities appeared, However, he could show no endometrial changes associated with chronic cystic mastitis. He further proposed that there is no relation between chronic cystic mastitis and the anterior pituitary. Whitehouse (21) stated the cause of chronic cystic mastitis is repeated cyclic hormonal stimulation, poor

breast drainage, and absorption of products of the hormone cycle.

Davis (27), in 1941, proposed the origin of chronic cystic mastitis to be action of gonadotropins of anterior pituitary, unopposed by estrogen. He points out that in hypophysectomized animals, the breasts atrophy, even though large doses of estrogen are given. He further points out that as ovarion function declines as menopause is approached, the pituitary is less opposed by estrogen, resulting in excessive amounts of gonadotropin. Since it is known that epithelial proliferation is the prime factor of the disease, Davis believes that it is not illogical to deduce that lack of estrogen, rather than increase, is the cause of chronic cystic mastitis. Morton (23), in 1946, continued along the lines Davis had previously proposed. He states that the anterior pituitary, as well as the ovaries, influence the breasts. However, the anterior pituitary may influence the condition of the breasts through ovarion stimulation, or lack of stimulation. He demonstrated that desoxycorticosterone is capable of replacing the stimulating effects of estrogen upon ductal growth. Morton quoting Turner (29) states, "F.S.H. stimulates estrogen release, which in turn stimulates the mammogenic factor of anterior

pituitary, which in turn stimulates breast hyperplasia". Morton concludes by saying that chronic cystic mastitis is the result of abnormal pituitary-ovarion relationship, and that this thus affects the breast.

Biskind and Biskind (24) blame poor liver detoxification for chronic cystic mastitis. It is their belief that the liver is the site of conversion of estrogens and androgens from physiologically active substancs to inactive substances. Inactivation of estrogen is controlled by factors which influence liver function, such as nutrition, poisons, and cirrhosis. Metabolism of androgens is not altered by such factors. Impairment of liver function thus causes alteration of estrogen-androgen equilibrium, favoring apreponderance of active estrogen. This condition leads to menometrorrhagia, premenstrual tension, cyclic painful breasts, and chronic cystic mastitis. Platt, Schultz, Kunstadter (25) pointed out that malnourished U.S. prisoners of Japan when placed on full diet often developed painful breasts that clinically and histologically appeared as chronic cystic mastitis. They proposed that the livers of these malnourished prisoners were unable to cope with the exogenous influx of estrogenic substance in the food because of long period of malnutrition.

Pullinger (26) agreed with the estrogenic preponderance theory, but he also brings out the fact that it is not merely an excess of estrogen but also the nature of the parenchyma of the breast that dictates whether or not chronic cystic mastitis will develop.

Elamon (27), in 1949, found that rats fed estrogens in amounts just consistant to maintain normal breast structure caused chronic cystic mastitis to appear. When the rats were thyroidectomized, feeding of thyroid extract prevented its appearance. From this work he concludes that chronic cystic mastitis is caused by a relative hypothyroid state, or else that the excess of estrogen surpresses the thyrotropic hormone of the pituitary. Ingleby (28) also points out that the thyroid may be an influencing organ. In 3 out of 18 cases studied, thyroid disease was found. Ingleby also noted that in the same 18 cases 16 had pelvic disease.

Broco and Sluczewski (29) refuted the work of men believing in hormonal imbalance. In a series of 50 cases they found variations of hormonal levels were so wide that no one hormone could be accused of causing chronic cystic mastitis. For example, hyperfolliculism was present in 60% of cases studied but 40% with similar lesions could not be explained on that basis. They suggest turning to

attempts to affect the local conditions of the breast by altering calcium, potassium, and other minerals in the blood.

PATHOLOGY

Under the heading of chronic cystic mastitis are found almost every benign lesion of the breast. Included are mastodynia, Schimmelbusch's "cystadenoma mammae" (3), adenomatous proliferation of Warren (4), "cystipherous desquamative epithelial hyperplasia" of Cheatle and Cutler (10), adenosis, fibroadenoma, papillomatous hyperplasia, mastopathic cystica, "blue-domed" cyst of Bloodgood (5), and senile hyperplasia.

There have been no definite breast types established that develop chronic cystic mastitis more than others. However, some generalities are observed more regularly than others. It has been found, for example, that mastodynia is present more in women from 30-40 years of age with well developed breasts. This same group is more likely to develop the mastodynia unilaterally. Women in 20-30 year bracket with small breasts are apt to develop mastodynia bilaterally. It is found that adenosis, or Schimmelbusch's disease, is more likely to occur in small, underdeveloped breasts. Large cysts develop more frequently in well developed breasts.

The incidence of chronic cystic mastitis is more than 50% less in married women with children than in nulliparous women. Interesting also is the fact that the more pregnancies a women experiences, the less the incidence of chronic cystic mastitis.

Approximately 50% of the lesions of chronic cystic mastitis occur in the upper outer quadrants, and both breasts are involved in somewhere between 1/3 and 1/2 of cases. Vanden Berg (16) further found that in 57 cases that the left breast was involved twice as often as the right.

Clinically, in the breast, is palpated a painfully nodular area with many small cysts detected, a shotty feeling to the area involved, or a single large cyst. The breast may or may not be painful. When it is painful it is usually worse before menstruation. Axillary glands may be enlarged and painful. Often the glandular portion of the breast involved may reveal no cysts at all and only pain is elicited.

The most conspicuous single fact, noted in microscopic examination of tissue from a chronic cystic mastitis patient, is epithelial hyperplasia. Hyperplasia may be classified roughly into five main groups; hyperplasia per se, adenofibrosis, benign parenchymatous

hyperplasia, precancerous hyperplasia, and cystic disease.

Hyperplasia is seen of epithelium of the glands, and/or the ducts, or both. The hyperplasia takes place in more or less an orderly manner with increase in number of cells lining the glands and the ducts. The cells may pile up, plicate locally, show numerical increase, variation in size and shape, and darker and larger nuclei. Fibrosis is increased in all areas affected. The ducts and glands are widened, especially the ducts. In some instances, small cyst like spaces measuring a few millimeters are seen. There is a diffuce lymphocytic infiltration seen in all affected areas. However, little importance has been attached to this.

Adenofibrosis clinically is palpated as a firm, perhaps tender, disc shaped breast, with saucer like edge, and occasionally palpable nodule. The whole breast need not be affected at one time and only one quadrant may show characteristic changes. Microscopically a great increase in connective tissue fibrosis is seen. This may proceed to such an extent that only remnants of glands and ducts are found in the affected areas. Rarely there are small cysts observable microscopically.

Benign parenchymatous hyperplasia clinically is palpated as numerous small nodules up to 15 millimeters in diameter which are firm but not fixed. Occasionally

cord-like structures representing areas of induration are found. Microscopically the predominant feature is proliferation of ducts, acini and connective tissue. The lumens of the ducts are full of secretary and epithelial debris. The epithelial cells show little variation from ordinary hyperplasia except for increased layering and sloughing of epithelial cells into the lumens of ducts and glands. It is in this group that approximately 50% of patients are found.

Precancerous hyperplasia gives the same picture as benign hyperplasia to palpation. Microscopically this condition resembles cancer. The cells are numerous, varied in size and shape, with hyperchromatic nuclei. The epithelium is layered, plicated, with many sessile papillary processes seen. Mitoses are common. There is, however, at no point evidence of the hyperplasia breaking through normal barriers.

Cystic disease, to palpation, shows one or more firm, well outlined, not fixed tumor mass. In this group is the typical blue-domed cyst of Bloodgood(9). Fluid taken from such a cyst is usually under pressure, thin, straw colored or cloudy. The lining of the cysts is flattened cuboidal epithelium which is layered and apparently degenerating. The wall is made up primarily

of connective tissue. These cysts are usually classified as entirely benign but malignant change has been known to occur in a very small percentage, especially if bloody fluid is found on aspiration.

The classification of chronic cystic mastitis lesions presented is primarily that of Cheatle and Cutler (10). However, all the types and classification of other authors may be fitted to it without destroying the separate authors work. This is done for clarification of material for a great number of names have been applied to the various portions of the disease.

DISCUSSION

A review of literature is of little value in determination of the question proposed. The investigators are virtually split on the subject. Some, as Bloodgood (6), have even reversed original opinions. Bloodgood, for example, submitted border line tumors to able pathologists in 1915 and the majority found them malignant. In 1930 he repeated this process and the majority of pathologists found the lesions to be benign.

It is admitted by most investigators in this field that chronic cystic mastitis is present in a very large number of women. The disease is not always clinically evident, but microscopic sections show the presence of

some form of the disease in a high percentage of breast tissue examined routinely.

Geschickter (15) quotes Barchardt and Goffe as finding evidence of chronic cystic mastitis in 93% of 100 patients over 40 years of age and clinically free from symptoms. He further quotes Franzas as finding evidence of the disease in 75% of 100 women between the ages of 18 and 98.

The coexistence of chronic cystic mastitis and carcinoma is also a matter of dispute. Some investigators, as Johnson (30) and Campbell (13), believe that since chronic cystic mastitis is so common microscopically that an evaluation on this basis alone is not valid in deciding whether the lesions are benign or malignant. They contend a history of clinically anticedent chronic cystic disease is necessary to establish such a conclusion. On the other hand, Cheatle and Cutler (10), Warren (3), Geschickter (15), Van Smith (31), Logie (14), and Coppleson (19) recognized the coexistence of the two lesions in varying percentage from 20%-80%.

It was attempted from the historical beginning of this question to prove, by such a coexistence and transitional changes to cancer, that chronic cystic mastitis is precancerous lesion. However, as there is no harmony

among pathologists as to a sharp borderline between benign and malignant the question appeared as a moot one. It seems that the words of Ewing (19) are very true. He stated: "No one has ever seen the beginning of a cancer." In recent years and with the advent of better equipment closer lines of division between benign and malignant are being drawn.

Because of the impossibility of arriving at definite conclusions, by means of the microscope, new methods were devised to study the problem. Warren (3) and Geschickter (15) in separate investigations delved into the death rates of women with chronic cystic disease, as opposed to the normal women.

Campbell (13), in 1936, did an extensive piece of work involving age, incidence, marital status, and follow-up period of 290 cases of chronic cystic mastitis. Since these patients were all diagnosed as chronic cystic mastitis before he contacted the cases, it remained for him to verify the diagnosis, analyze the material and follow the case for as long as possible.

Campbell made the assumption that most have made working in this field. He believed chronic cystic mastitis to be diffuse process. In his series of 290 cases, 233 had local excision of the lesion and 57 had simple unilateral mastectomy.

In an analysis of the cases, Campbell found the maximum age of chronic cystic mastitis to be between the ages of 40 and 45 in nulliparous women. He found 22% of all chronic cystic mastitis occurred during this period. The graph presented in figure I shows not only the age incidence of chronic cystic mastitis but an analysis of 8,053 cases of carcinoma of the breast as composed by Lane-Claypan and presented by Campbell.

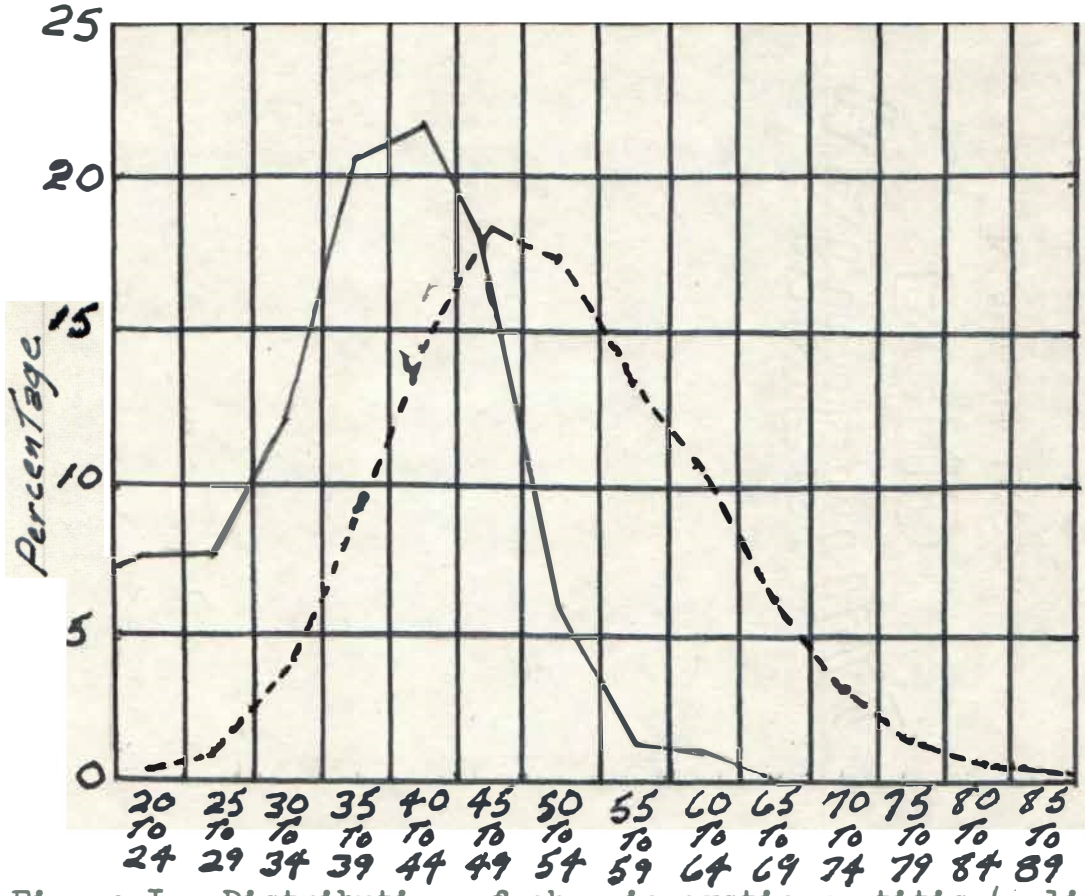

Figure I. Distribution of chronic cystic mastitis (solid line) and carcinoma (broken line) by age.

Campbell contends that clinical evaluation and not

pure microscopic studies should be given more weight in the judgement of malignancy. In this series of 290 cases only 2 developed carcinoma followed an average of 10 years. He therefore concludes: "Cystic disease is not a precancerous lesion and malignant changes are no more likely to develop in a breast showing the disease than in one which is entirely normal." He further states: "The adenocystic disease is no more dangerous than the simple cystic form."

Geschickter and Lewis (12), in 1935, surveyed 1,038 cases of chronic cystic mastitis and concluded the lesion was benign. Warren (3) however, points out that in the series of cases run by Geschickter and Lewis that the average age was 38 which he states is not within the predominate age for attack by cancer. Warren quotes the work of Bigilow and Lombard in 1938 as pointing out the fact that the average age of patients affected by carcinoma is 60 years of age.

Geschickter (15), in 1943, in a series of cases totalling over 1000 found that the average age of cases of the grossly cystic type of the disease were between 40-45 years of age, adenosis between 35-40 years of age, and mastodynia 35-40 years of age.

It is granted by almost 100% of investigators that women who have born children are less apt to develop

chronic cystic mastitis than are nulliparous women. It is further found that women who have more than one child further reduce the chances of developing the disease. There are many cases of sterility and menstrual disorders recorded in women who are afflicted by chronic cystic mastitis. This is thought to be due to endocrine imbalance with predonderance of estrogen over corpus luteum. It is not unlikely, as was concluded by Morton (28), that pregnancy is a cure for the disease. This has proved to be clinically true.

The next step in proving or disproving the question, is to determine the percentage of women developing cancer in the normal population. Warren (3), in 1941, and Geschickter (15), in 1943, tabulated such evidence. Warren computed incidence of carcinoma in Massachusetts in the years 1928-1932 and Geschickter with the help of Dr. Louis I. Dublin, Third Vice President and Statistician of the Metropolitan Life Insurance Company, on a national basis for the years 1933-1936. The figure of the two investigators are practically the same. Only Geschickter will be shown.

AGE GROUP	DEATHS	DEATH RATE/100,000
30-34	646	5.0
35-39	1,633	13.5
40-44	2,817	24.1
45-49	4,046	39.5
50-54	4,875	55.6
55-59	5,080	69.2
60-64	4,925	86.0
65-69	4,337	99.0
70-74	3,486	114.0
75-79	2,655	141.0
80-84	1,493	164.4

Death and death rate per 100,000 from cancer of the breast.

By these figures it is possible to arrive at an average age of patients attacked by carcinoma. The figure arrived at by Dublin is 40 years of age. It was further calculated that expected number of cases of mammary carcinoma in the general female population (average age 40 years) is 42 per 100,000 or .42%. On this basis Geschickter figured that in 793 cases he followed, there should be 3 or 4 cases of cancer. Among the cases, followed by Geschickter for ten years, 10 developed cancer or an incidence of 1.26%. However, he believed that since only 7 died with metastasis only these should be counted in the tabulation. This reduces the cancer rate in chronic cystic mastitis to 0.88% which is roughly twice the incidence of carcinoma in normal women. Geschickter further breaks the figures down showing that incidence in adenosis is 2.% or 5 times expected figure,

cystic disease is 0.79% or twice expected rate, and the rate of attack in mastodynia was zero.

Warren (3) in a study compared the attack rate by carcinoma of women in the state of Massachusetts with chronic cystic mastitis against women without preexisting disease of the breast. To compute this figure, Warren included in his figures cases of chronic mastitis, (hyperplasia) 173 cases; chronic cystic mastitis, (benign parenchymatous hyperplasia); adenosis, 340 cases; adenocystoma (intraductal, papillary growth) 21 cases; and adenofibroma, 70 cases. To find the average attack rate of carcinoma of the breast in women without preexisting breast disease he found the death rate of women in Massachusetts to be 78.1 $\pm$ 6.4 per 100,000 for women single and over 30 years of age, and 55.5 $\pm$ 2.5 per 100,000 for those not single over 30 years of age. Doubling the death rate all females (29.7 per 100,000)and those over 30 years of age (59.3 per 100,000) he arrives at a figure of 0.06% for all women in the state of Massachusetts and 0.12% for those over 30 years of age.

Of the total of 604 cases of cystic mastitis studied, 30 or 2.6% developed cancer. This was found on the basis of an average of 9.3 years follow-up study. Carcinoma developed in 11 of the 173 cases of chronic mastitis;

14 in 340 cases of chronic cystic mastitis; 3 in 21 cases of cystastenoma, and 2 in 70 cases of adenoma.

Of the group studied, the ages ranged from under 29 to over 80. 372 of these cases were between the ages of 40 and 60, and 349 were over the age of 50. This enabled the author to have a suitable number of cases in the cancer age.

Warren observed that any increase in deaths of women with preexisting chronic cystic mastitis due to cancer is certain proof that this condition predisposes the disease to cancerous change. Calculating risk years involved by multiplying the number of cases by the average length of follow-up and comparing them to a normal group for a similar length of time he concluded that chronic cystic mastitis predisposed to cancer 4.5 times as great as the normal women. He further found that women under 50, or before menopause, who have preexisting chronic cystic mastitis are more likely than those past the menopause to develop carcinoma than the normal female population.

SUMMARY

A survey of the past history of chronic cystic mastitis from 1845 leads to no definite conclusions in the answer to the question; benign or malignant? Among the authors surveyed by this thesis, eleven were of the opinion that the

disease is predisposing to malignant change while eight are of the opinion that it is completely benign. Until 1936 most of the work done in this field, in determining the status of lesions, was done with histologic sections. By this means, pathologists were split in their decisions. Bloodgood (6) for instance, submitted a series of sections to pathologists in 1921 and again in 1930. The predominance of diagnosis in 1921 was malignant lesions, whereas in 1930 the majority stated the lesions were benign. Campbell (13), in 1936, approached the problem entirely from a diagnosis and follow-up study direction. Geschickter (15) and Warren (3) not only followed the work of Campbell but advanced the knowledge to some extent by computing the death rate of women with chronic cystic mastitis as compared to women whose breasts are normal.

Campbell in a series of 290 cases followed for an average of ten years, found only 2 developed carcinoma. On the basis of his clinical observations and follow-up studies, he believed chronic cystic mastitis to be a benign disease. Geschickter and Warren, on the other hand, found the disease to predispose to cancer.

Geschickter, with the aid of a statistacian, calculated the incidence of carcinoma in women without pre-

existing chronic cystic mastitis. They found an average age to be 40 and an attack rate to be 42 per 100,000. In a series of 793 cases diagnosed as chronic cystic mastitis both clinically and histologically, he found a total of 10 carcinomas. This is a percentage of 1.26 as compared to the normal women of 0.42. On this basis he pointed out that chronic cystic mastitis predisposes to carcinoma 3 times as much as women without preexisting chronic cystic mastitis.

Warren analyzed 604 cases of preexisting chronic cystic mastitis in an attempt to prove the predisposition of the disease to cancer. The average length of follow-up was 9.3 years. The distribution of cases by age was compatible to place one-third between the ages of 30-40 and one-half between the ages of 40-60. Of the total of 604 cases 30 developed carcinoma. He then compared this to the attack rate of all women of the state of Massachusetts over age 30. The attack rate of all women over 30 years of age in the state was found to be 1.2 per 1000. The cases Warren followed proved to have an incidence of 5.8 per 1000. In a further break down of figures, Warren found between the ages of 30-49 years, carcinoma developed in 5.96 ± 1.80 as compared to the female population of 0.50 ± .03 or 11.7 times as great. In cases over 50,

the rate in the studied group was less, 5.23 ± 1.23 as compared to the Massachusetts female population of 2.11 ± 0.07 which is still 2.5 times that found in women without preexisting chronic cystic mastitis. In totalling all cases he calculated that preexisting chronic cystic mastitis predisposes to carcinoma 4.5 times as often as the normal female breast.

CONCLUSIONS

1. Etiology of the disease is as yet undetermined.
2. A study of early investigators work is insufficient to answer the question as to the predisposition of chronic cystic mastitis to cancer.
3. Histologic studies are unable to prove the answer to the question of benign or malignant, due to wide differences of opinion of pathologists.
4. Follow-up studies of previously diagnosed cases of chronic cystic mastitis is the best method of proving whether the disease predisposes to cancer if an adequate control group is run on normal females in large numbers.
5. On the basis of good follow-up studies and adequate control groups, of Geschickter and Warren, chronic cystic mastitis predisposes to cancer somewhere between 3 and 4 times as often as is found in the normal female population.

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