

PAGET'S DISEASE OF THE MALE BREAST*

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IN 1874 SIR JAMES PAGET described a rather unusual type of eczema of the areola and nipple which was invariably succeeded by cancer of the underlying breast during the next year or two, and in so doing Paget delineated a clinical condition which came to bear his name. Some 15 years later Darier first described the histologic appearance of the large clear cells in the eczematous areola which today are termed Paget cells. During the ensuing years many controversial points of view have been expressed concerning the true nature of this peculiar areolar eczema, and its relation to the underlying breast cancer. Because there is no unanimity of opinion even today, plus the fact that this condition in the male breast is extremely rare, we have felt it proper to review the subject of Paget's disease of the male breast and present a case report along with pathologic studies.

HISTORICAL

Paget's original paper was purely a clinical description of areolar eczema followed by breast cancer, based on a series of 15 women. This report made no mention of any histologic data. As has been cited above, it was Darier who in 1889 first reported on the histopathology of the areolar eczema and the associated breast carcinoma. After a review of the literature we have been able to find only four cases of Paget's disease of the male breast which have been adequately confirmed by micro-

scopic studies. The mere presence of eczema of the nipple and an underlying breast tumor does not make for the diagnosis of true Paget's disease. Two microscopic criteria must be satisfied, namely the presence of Paget's cells in the epidermis of the areola and ductal carcinoma of the underlying breast parenchyma.

Elbogen in 1908 cited a case with metastases in the axillary nodes. The patient succumbed to his disease one year after radical amputation of the breast. Jonas described a male who had bilateral involvement of areolae and breasts. This patient succumbed one year later to extensive metastases. In 1917 Sekiguchi wrote an excellent paper on Paget's disease in which he cited one case occurring in the male. On the basis of his studies he pointed out that the Paget cells are seen in greatest numbers in the neighborhood of the outlets of the lacteal ducts and are confined to the areola. Sekiguchi further observed that the Paget cells, unlike epidermal carcinoma cells, did not appear to invade the corium. He concluded that Paget cells represent "regressive" migrated carcinoma cells in the epidermis taking origin from the underlying and closely adjacent primary breast duct carcinoma. This point of view, which was later championed by Muir and represents one popular school of thought today, did not coincide with the prevailing opinion as originally expressed by Darier in his classical description of the Paget cells. Darier believed that

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Paget's eczema of the nipple represented a form of dyskeratosis.

One of the most frequently quoted instances of Paget's disease in the male breast is a case which occurred in a 35-year-old Sudanese, reported by Archibald. He described "Paget's cells" which were located in the epidermis adjacent to an ulcerative focus in the right nipple. Study of the author's photomicrographs raises considerable objection to its acceptance as a *bona fide* instance of Paget's disease, although a relatively high grade breast carcinoma with skin ulceration cannot be denied.

From a review of the records at the Mayo Clinic, Rubenstein came upon one instance of Paget's disease occurring in the male breast. This man of 57 years gave a history of soreness of the nipple for two years. Examination revealed an ulcerated nipple without any palpable mass in the breast. Simple mastectomy was performed and five years later the patient was reported as well. Histologic study revealed ductal breast carcinoma with Paget cells in the areola. Following an extensive review of the literature, Rubenstein concluded that Paget's disease represents a dyskeratotic cellular change in the epidermis which may be precancerous in some cases. He conceded that removal of the breast is the proper procedure in the therapy of Paget's disease. It is sufficient to say that despite its controversial histogenesis all authors today agree that Paget's disease of the areola is a truly malignant neoplasm of the breast requiring radical mastectomy.

CASE REPORT

Mr. M. W., 55 years old, was admitted on November 28, 1950, to the Syracuse General Hospital. The patient (previously in good health and actively employed as a city fireman) first became aware of mild soreness and swelling of the left areola one year prior to admission. Intermittent swelling of the areola continued for a period of 6 months and was attributed by the patient to local irritation from his cigarette case which he carried in his left breast shirt pocket. Beginning several

months before, the patient noted the affected nipple and areola to be the site of superficial weeping and bleeding. He consulted a physician who prescribed local medication for the areola eczema. While on this local therapy the areolar lesion would heal almost completely, only to ulcerate again. Because of a chronically infected pilonidal sinus the patient consulted another physician who referred him to one of us (E.L.S.) for surgery. The patient had suffered no loss of weight, and his review of systems was essentially negative. One aunt and sister had died of cancer of undetermined origin.

Examination revealed a well developed and well nourished male in no apparent distress. The left areola and nipple were involved in a chronic eczematoid process characterized by increased pigmentation of the areola, superficial ulcers with some crust formation, and considerable distortion of the nipple. There was no mass palpable beneath the areola, nor was gynecomastia evident. The opposite breast was normal. Several enlarged firm glands were palpable in the left axilla. The sacrococcygeal region was the site of a typical chronically infected pilonidal sinus. The blood cell count and the roentgenogram of the chest were within normal limits.

On the day following the patient's admission to the hospital the affected left nipple and areola were totally excised. Subjacent to the areola, no breast parenchyma was evident grossly. The preoperative clinical impression of possible Paget's disease was not borne out at the time of the original frozen tissue examination. Accordingly, a wide excision of the pilonidal sinus was performed, since the patient's chief complaint was referable to the latter.

Upon examination of the permanent paraffin sections of the excised areola, the diagnosis of Paget's disease of the breast became apparent. (See pathology report below.) The patient was then returned to the operating room and a classical radical mastectomy was performed through a long transverse incision. As the dissection proceeded, it was quite obvious that there were many regional nodes involved by metastatic cancer. The nodes in the lateral thoracic group, along the lateral border of the pectoralis minor, were unusually firm and markedly enlarged. The patient was discharged from the hospital ten days later. Superficial necrosis of the wound edges in the extreme lateral angle of the wound was a minor complication in the postoperative period. About one month following mastectomy, the patient was referred to a radiotherapist, who administered deep roentgen ray therapy to the left axilla and left supraclavicular region.

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Pathologic Findings. The first surgical specimen (50-5100) submitted on November 29, 1950, measured 4.5 x 3 x 2 cm. and consisted of skin, including the nipple and areola, and some underlying subcutaneous and breast tissue. The ecze-

matoid, crusted type of lesion described above was noted on the external surface and no areas of thickening were palpable within the tissue. Microscopic examination revealed the presence of numerous so-called Paget's cells within the epidermis and

FIG. 1

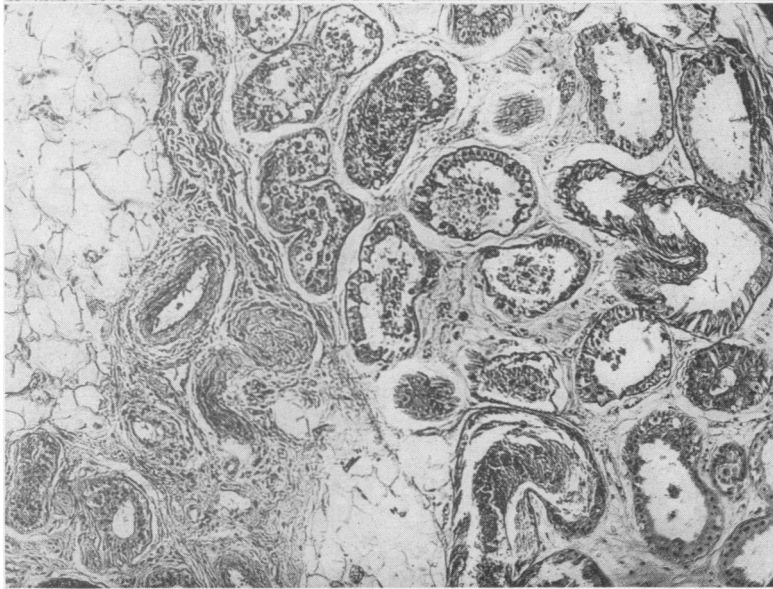
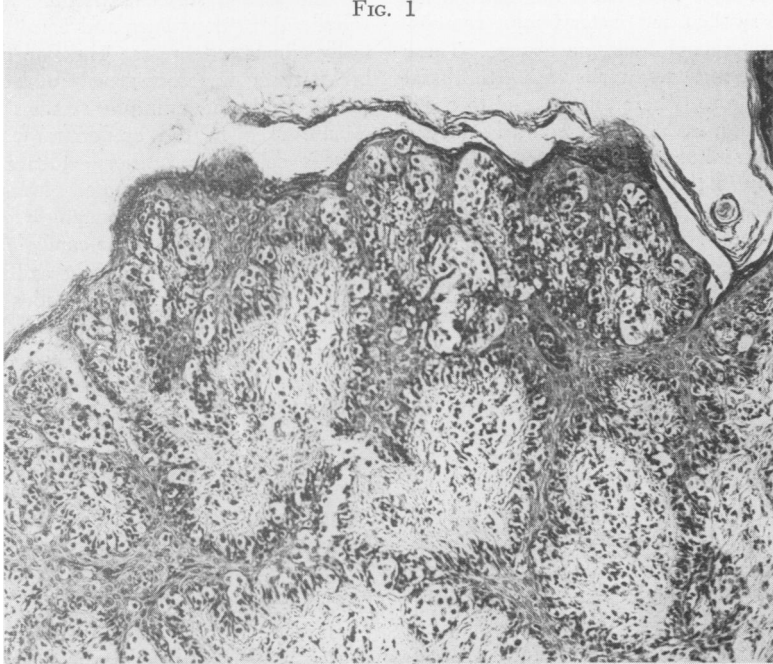


FIG. 2

FIG. 1.—Nipple area showing "Paget's cells" distributed throughout the epidermis and at the epidermal-dermal junction (x 110).

FIG. 2.—Dilated, actively secreting, apocrine sweat glands. Eccrine glands can be seen in the lower left corner (x 95).

in the papillary layer of the dermis (Figure 1). These large oval cells, which varied moderately in size and shape, contained a vesicular nucleus with a prominent acidophilic nucleolus. The most characteristic feature of the cells was the cytoplasm which was sometimes reticulated but more often appeared pale, swollen and watery, most reminiscent of cells undergoing hydropic change. These Paget's cells were most numerous within the basal layer of the epidermis, where they tended to occur in clusters, although isolated cells could be identified in the upper stratum spinosum, stratum granulosum and rarely in the stratum corneum. In the affected areas the epidermis was thickened and revealed evidence of both hyperkeratosis and parakeratosis. The rete pegs were slender and elongated and large number of lymphocytes and plasma cells were noted at the junction of the epidermis and the dermis.

Alterations were also observed in the dermal appendages, with Paget's cells being identified along the external root sheath of many hair follicles. Slight secretory activity was noted within the eccrine sweat glands but the glandular and ductal epithelium showed no abnormal cellular changes. The apocrine sweat glands, however, were dilated, irregular in shape and manifested marked secretory activity (Fig. 2). This was evidenced by the basal location of the glandular nuclei and the accumulation of granular cytoplasmic material at the luminal surface of the cell, producing a bulging appearance. The glandular lumens contained desquamated cells and large amounts of acidophilic granular secretory material. Because the mammary gland is considered to be a modified sweat gland, and since Weiner's concept of an apocrine cell carcinoma origin for extramammary Paget's disease has been so universally accepted, special attention was focused upon the apocrine sweat gland structure. The apocrine epithelium, however, showed no changes suggesting any relationship between the epidermal pathology or the ductal carcinoma described below.

One of the sections taken from the sub-areolar area demonstrated the presence of a small focus of invasive carcinoma (Fig. 3). These tumor cells contained large hyperchromatic nuclei, scant basophilic cytoplasm, and tended to arrange themselves in cords separated from one another by dense connective tissue stroma. Similar cells were identified within several ducts adjacent to this small area of invasion (Fig. 4). This block was serially sectioned in an attempt to establish direct continuity between the intraductal lesion and either the overlying Paget's cells or the infiltrative lesion beneath. Despite our failure to establish a continuity be-

tween the three areas by means of this technic, the histologic appearance of the intraductal and nearby infiltrating tumor cells is similar enough to justify the diagnosis of a rather early invasive lactiferous duct carcinoma.

The second surgical specimen (50-5241) was submitted 10 days later and consisted of the radically amputated breast. The skin and underlying breast tissue were not grossly unusual, but microscopic study of multiple sections disclosed one minute area in the epidermis which contained Paget's cells. No further evidence of ductal or invasive carcinoma was noted. Many firm, greyish colored lymph nodes averaging around 1 cm. in diameter were found in the coraco-clavicular fascia and in the apical portion of the axillary fat. Microscopic examination of these nodes revealed each one to be nearly completely replaced by metastatic tumor which was of the mucin-producing variety (Fig. 5). Clumps of malignant tumor cells similar to those described within the lactiferous ducts appeared as though suspended in this mucinous material. Many of the individual cells had a foamy vacuolated cytoplasm with nuclear compression, giving them a signet ring appearance (Fig. 6). Aggregations of tumor cells were seen within the lumens of several arterioles in the peri-nodal connective tissue. The presence of mucin in the lymph nodes was confirmed by the use of Mayers mucicarmine stain which revealed large amounts of this material within the tumor cells and in the extracellular fluid. At this point it was thought worthwhile to stain similarly sections of the epidermis in an attempt to demonstrate the presence of mucin within the Paget's cells, but the results were consistently negative.

DISCUSSION

Few pathologic lesions present as distinctive a microscopic picture as does Paget's disease of the breast. As Allen has pointed out, the junctional nevi and melanomas bear enough resemblance to Paget's disease to lead occasionally to a mistaken diagnosis. He states that instances in which no carcinoma is found in the parenchyma of the radically resected breast with presumed Paget's disease should be re-examined for evidence of junctional nevi or small melanomas. Because the lesions are cytologically identical within the cutaneous junction zone, and since there is often lack of demonstrable melanin pigment in junctional

nevi and pagetoid melanomas, the only reliable criterion for the diagnosis of Paget's disease is the presence of undisputed intraductal carcinoma. It is to be emphasized

that single sections are frequently negative or at most suspicious, so that the study of a great many blocks may be necessary to find such a focus of carcinoma. Additional sup-

FIG. 3

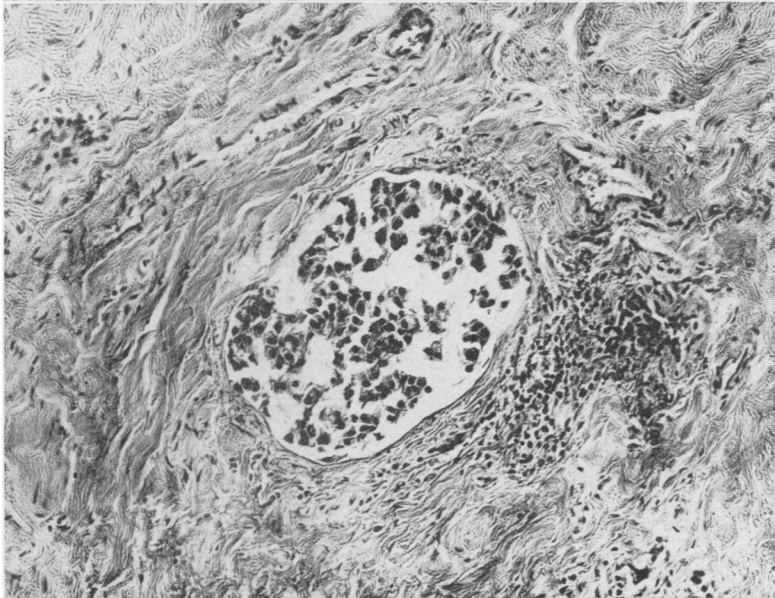
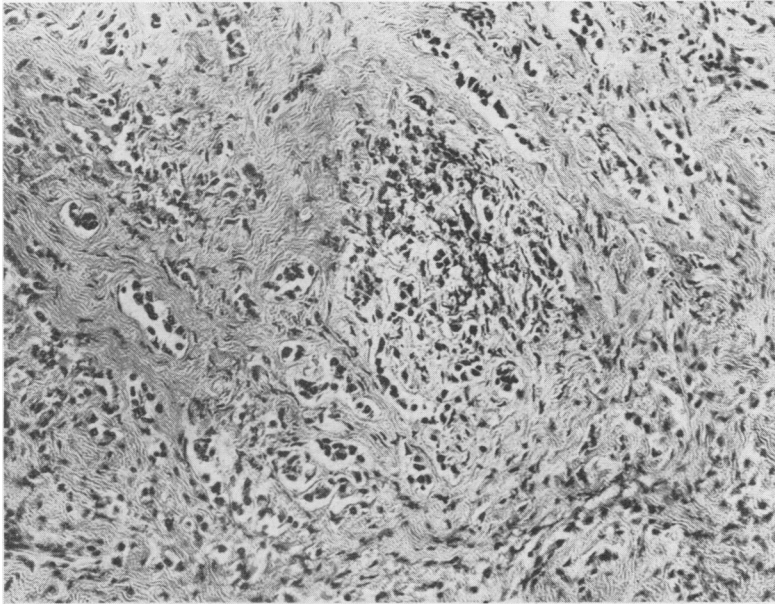


FIG. 4

FIG. 3.—Infiltrative carcinoma growing in cords separated by dense connective tissue (x 125).
FIG. 4.—Sub-areolar lactiferous duct nearly occluded by carcinoma cells (x 160).

portive evidence in the case herein reported was the finding of early dermal infiltrative carcinoma and the presence of the mucinous character of the nodal metastases.

Majority opinion today contends that Paget's disease of the nipple represents epidermal extension from an underlying lactiferous duct carcinoma. That this thesis is not universally accepted is shown by a recent article from the Mayo Clinic. In this paper the authors, Watkins and McDonald, state that Paget's disease represents an *in situ* squamous cell epithelioma of the skin of the nipple, always associated with intraductal carcinoma of the breast parenchyma. Other investigators, not willing to indict two separate neoplasms, feel that the condition can be satisfactorily explained by a primary epidermal carcinoma having origin in the cells of the rete malpighii. In this connection Foote and Stewart have pointed out that if Paget's disease is primarily epidermal in origin, it is peculiar that the infiltrating tumor does not commonly assume the form of an epidermoid carcinoma in both the primary tumor and its metastases.

While the present study has contributed little to our knowledge of the histogenesis of the Paget cell, one observation may be pertinent. This concerns our failure to demonstrate mucin-producing qualities within the epidermal Paget's cells despite its presence in large amounts in the lymph nodes. It must be stated, however, that while it is not unusual for metastatic lesions to show considerable histologic variation from their primary tumor, contiguous areas of carcinoma, such as the epidermis and ducts, should be similar. This line of reasoning prompted the investigation of Paget's cells by means of the mucin stain, using cases of Paget's disease in the female from our files. The results of this study are interesting because we were not able to identify mucin within the epidermal or junctional Paget's cells in these cases, al-

though significant amounts were often noted within the subjacent ductal carcinoma cells. Thus it would appear that the proponents of the ductal theory of origin for the Paget's cells must advance some explanation for an incongruous loss of mucin-producing ability once these cells have invaded the epidermis. Perhaps such inconsistency may be due to the regressive metamorphosis of the ductal carcinoma cells which Sekiguchi claims occurs during their migration in the intercellular lymph channels of the epidermis.

Despite the confusion concerning the precise pathogenesis of Paget's disease, there can be no argument that from the clinical point of view this condition must be regarded merely as a variant of true breast cancer. In a series of 967 cases of breast carcinoma reported from Copenhagen⁹ 24 were found to be examples of Paget's disease—all occurring in women—an incidence of about 3 per cent. The general figure of somewhat less than 1 per cent usually is given to express the incidence of cancer of breast in the male as compared to the female. With these figures in mind one can readily anticipate the rarity of Paget's disease in the male. In a series of 9279 breast pathologic examinations performed at the State Institute of the Study of Malignant Disease in Buffalo,¹¹ 60 instances of cancer in the male were discovered, none of which were considered to be Paget's disease.

Wainwright in an exhaustive study of carcinoma of the male breast was one of the first to point out the poorer prognosis of breast cancer in male as compared to the female. He cited the figure of 19 per cent five-year survival. Some years later Sachs confirmed Wainwright's observation regarding the prognosis of cancer in the male breast. In a series of 178 cases, collected from all over the United States and Canada, Sachs reported that simple mastectomy had been performed in 22 per cent of the cases. This, of course, represents inadequate sur-

FIG. 5

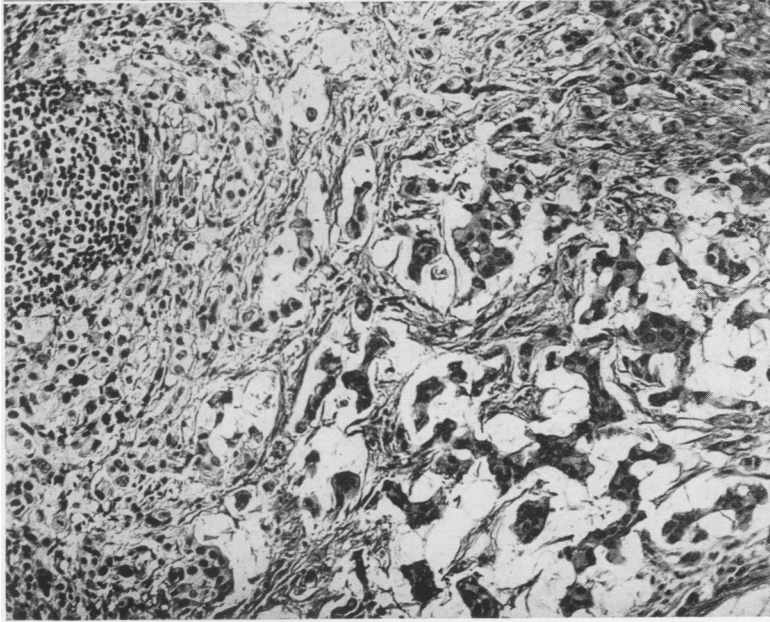
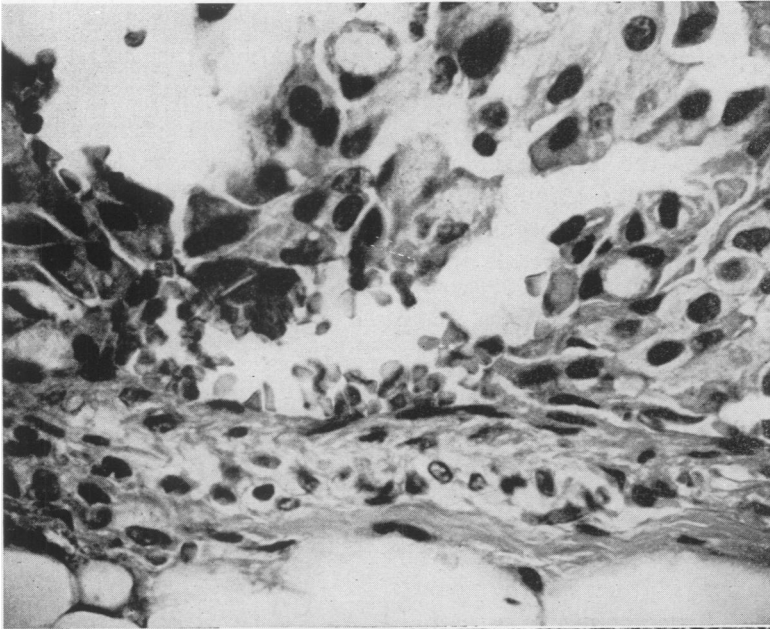


FIG. 6

FIG. 5.—Peri-nodal arteriole containing large numbers of tumor cells. The signet-ring appearance of some of the cells is particularly prominent (x 550).

FIG. 6.—Axillary lymph node almost replaced by metastatic carcinoma which is of the mucin producing variety (x 150).

gery and perhaps explains in part the poor survival rate. It would appear that not only is the laity unimpressed with the possibility of breast malignancy in the male, but that the medical profession is equally lax by reason of their failure to carry out the necessary radical surgery.

Charache shares the feeling of many authors that trauma plays a significant role in the etiology of breast cancer in men. (Our patient believed his breast eczema was attributable to constant irritation from a cigarette case carried in his breast pocket.) The combination of greater exposure to trauma experienced by men in general in contrast with women, plus the more superficial nature of the male breast, probably accounts for this clinical impression which is completely without scientific basis. As was pointed out by Charache, cancer of the male breast is characterized by a higher incidence of nipple ulceration and invasion of the pectoral fascia as compared with the female breast. The degree of neoplastic invasion beyond the confines of the female breast is less by virtue of the bulk of the female mammary gland. This fact was borne out in our case as shown by the massive invasion of the pectoral nodes lying in the pectoral and coracoclavicular fascia.

Geschickter implies that those cases of Paget's disease with absence of a clinically palpable breast tumor have a better prognosis than those in which there is an associated palpable tumor. This belief cannot be borne out in our case where, in the absence of a palpable mass, the lymph nodes were involved by metastatic cancer to a marked degree. Costello reviewed 29 cases of Paget's disease occurring in women. In 12 of the 29, no breast mass was clinically noted in association with the areolar lesion, and yet some of these patients had metastatic lymph node metastases. Costello theorized that the primary breast tumor remained microscopic in size for a long time

because it had become "quarantined by fibrous tissue." It goes without saying that all cases of nipple and areola eczema refractory to treatment should be biopsied even when no subjacent breast tumor is palpable. Moreover, the suspicion of Paget's disease should not be abandoned despite the long history of areolar eczema. In Costello's series, the duration of the eczema was greater than one year in half of the cases. Paget's disease, generally speaking, occurs in a somewhat older age group than does ordinary breast carcinoma, and its natural history may therefore be expected to be more protracted.

SUMMARY

A case of Paget's disease of the male breast is reported—the fifth in the literature with acceptable pathologic verification.

The histopathology of this condition is discussed and illustrated. The result of a special study of the so-called Paget's cells with the use of mucin stains is presented.

Biopsy of any areolar eczema proving refractory to local therapy is most important, even in the absence of a palpable mass in the underlying breast. Paget's disease of the areola is a malignant breast lesion which can be properly treated only by radical mastectomy.

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