More than sixty years has elapsed since Sir James Paget (1), with admirable succinctness, described a peculiar affection of the skin now called Paget's disease of the nipple. Paget himself had noted the possibility of an extramammary location, and his casually created dichotomy of mammary and extramammary has persisted to the present time, even though, before long, the histologic identity of the lesions became evident. The proper justification for maintaining this division was the number of clues which the extramammary cases might offer towards the solution of this long baffling affection. For the history of the disease, as recorded in a voluminous literature, is a history of prolonged controversy. Is Paget's disease a chronic eczema? Is it a dyskeratosis, or precancerous? Is it always associated with cancer? Is it itself cancer? If so, what sort of cancer? These and a host of similar questions regarding both the etiology and histogenesis have been raised constantly. Unfortunately, the answer—presumably histological—has too frequently been sought in either clinical or incomplete surgical material. Of the 57 extramammary cases recorded in the literature, not a single one includes necropsy findings. Such a situation in turn has tended to discredit a method inadequately utilized. Cheatle (2), himself an advocate of a more complete histological technic, says: "... morphological appearances alone are insufficient to determine beyond all doubt the site of the epithelium in which the neoplasia originated. Whether unanimity of opinion on this matter will ever be reached does not concern the problem. . . ." That such a view is not justified has been amply demonstrated by many of the more recent detailed studies, as those of Muir (3), Pautrier (4), and Simard (5).

In the belief that the histogenetic mystery of Paget's disease might be elucidated by detailed histological studies, the following case, occurring in the vulva, was studied. As the study progressed, it became increasingly evident (a) that the extramammary site was not completely haphazard, (b) that the relation between the skin lesion and the underlying cancer was fairly definite, and (c) that the nature of the carcinoma could be determined with reasonable certainty. Furthermore, interesting general relationships were discovered between the apocrine sweat glands and Paget's disease.

Case Report ¹

E. F. J., widow, eighty-four years. The family history was notable for longevity. Besides the usual childhood diseases, the patient had had a laparotomy in 1915 for the release of adhesions causing partial intestinal obstruction, Ménière's syndrome since 1900 with

¹ Dr. Wilder Tileston, whose private case this was, very courteously supplied the clinical history, abstracted below.
progressive deafness, a transient “shock” in 1924 with aphasia followed by a slightly elevated blood pressure (170/85). During the last year of life she had shown evidence of senility—childishness, forgetfulness, and occasional mental confusion.

Since 1928 the left side of the vulva had shown a “patch of eczema with lichenification” (Dr. John Lane’s notes). This was treated continually, and in October 1934 it was noted that each labium majus was red and excoriated. About six months before death an indurated nodule, 2 cm. in diameter, was observed on the left greater labium, and about 8 indurated papules were discovered in the left groin. Beginning in May 1936 there was severe but inconstant pain in the right lower quadrant and right flank. On May 5 the liver was found somewhat enlarged and hard, reaching 2 cm. below the ribs in the right mamillary line and 5 cm. below the xiphoid process. Jaundice was absent throughout. For the last week of life the patient refused nourishment. She was in stupor during the last three days with frequent twitchings of the right shoulder but no other neurological abnormalities. Death occurred July 13, 1936.

**Gross Necropsy Findings:** The body was that of a well developed elderly woman. Emaciation was not marked despite the long illness. The skin was pale and atrophic. There was no jaundice. Scattered over the surface of the chest, abdomen, and back—most abundantly in the axillae, upper chest, and back—were large numbers of typical senile (seborrheic) warts, running the gamut, in appearance, from dull yellow, opaque, slightly greasy flat elevations to raised, irregular, dark brown, coarsely furrowed excrescences. These varied from several millimeters to more than a centimeter in diameter and were not infrequently confluent. No induration or ulceration was observed. The superficial lymph nodes, except in the left groin, were nowhere palpably enlarged. Slight pitting edema was present over both tibiae and ankles. The breasts were small, flat, and soft with no palpable masses. The flattened nipples revealed no abnormality.

The vulva presented a remarkable appearance. Both labia majora and minora, but especially the left, were diffusely swollen and indurated. The inner and part of the outer surfaces of the labia majora were intensely reddish-purple and velvety, an appearance which extended to the clitoris and the labia minora. Demarcation of the involved areas from the uninvolved skin was relatively distinct. The involved surface was moist and oozing, spotted with numerous adherent, grayish-yellow, opaque flakes, presumably epidermal. The introitus proper was parous and there was no discharge. In the anterior portion of the left labium majus, slightly caudad to the mons pubis, a stony-hard mass was palpable, about 2 cm. in diameter, projecting slightly above the surface and extending into the deeper tissues. The overlying skin, to which it was attached, was slightly bluish, but nowhere ulcerated, although it merged peripherally with the patch of “eczema” mentioned above. About a dozen firm gray papules, several millimeters in diameter, projected from the skin of the left groin on either side of Poupart’s ligament as well as on the medial and lateral aspects of the left thigh. These papules were attached to the overlying skin. The left inguinal lymph nodes were slightly enlarged and shotty. The femoral nodes were not palpable. No comparable lesions were found in the right groin.

No free fluid was present in the peritoneal cavity. The pelvic cavity was infiltrated in many directions by an irregular mass of firm, gray-white tumor tissue. The adnexa on the right, curiously enough, were invaded, while those on the left were free. The iliac, hypogastric, lumbar, and aortic lymph nodes were so extensively invaded as practically to encase the aorta and its major subdivisions. The extension of the tumor along the aorta was found as far cephalad as the ligament of Treitz, and numerous abdominal and pelvic lymphatic channels were outlined by series of submiliary tumor nodules, like strings of beads. The extensive encirclement of the iliac vessels by tumor probably accounted for the edema of the lower extremities. Both ureters were rigidly encased in tumor from their sites of entrance into the bladder to the ureteropelvic junctions.

The pelvic organs were examined for the nature of the metastatic spread. Nothing abnormal was seen in the bladder; and in the rectum only a few non-ulcerated internal hemorrhoids. The vagina was lined by a smooth, glistening atrophic mucosa and the wall proper was not perceptibly thickened. The cervix was small; it showed a few old scars, several small nabothian cysts and some scanty yellow but clear mucoid secretion at the os. The uterus was small; on section, numerous hyaline areas and obliterated vessels were seen
in an otherwise uniform myometrium. The slightly enlarged endometrial lumen was lined by pale, smooth mucosa. In the region of the right cornu was a sessile, oval, glistening cystic polyp, 1.5 cm. in diameter, of the type frequently seen in the senile uterus. The adnexa on the left were not remarkable; the ovary was small, ovoid, and covered by a glistening, gray-white, corrugated tunica albuginea; the fallopian tube was thin with free fimbriated edges, and the broad ligament thin and glistening. In contradistinction, the right uterine margin was infiltrated by tumor and the isthmus invaded; the broad ligament was thickened and shortened; the fallopian tube was thick and irregular and the ovary largely replaced, its parenchyma pushed aside by the gray-white firm tumor tissue.

Contrary to Handley’s view, where carcinoma in the lymphatics is most extensive, Paget’s disease of the overlying skin is least noticeable. The epidermis is compressed; there is moderate hyperkeratosis. “Paget cells” are absent. A short distance away, as the underlying tumor grows smaller, “Paget cells” appear in increasing numbers. Note vacuoles in carcinoma cells. × 90.

The liver weighed 1330 gm.; its surface was distorted and its dark brown parenchyma compressed by numerous oval or round umbilicated metastases, varying in size, the largest (7 × 6 cm.) almost replacing the left lobe. The tumor tissue proper was gray-white, firm, elastic, and on cut surface not quite homogeneous; spots of red and opaque yellow, suggestive of hemorrhage and necrosis, alternated with irregular translucent areas. An occasional irregular translucent tumor nodule was found in the adrenal medulla. In the left pleural cavity a stony-hard mass involved the paravertebral portion of the 6th and 7th ribs. This mass, several centimeters in diameter, projected about 0.5 cm. above the surrounding pleural surface; the overlying pleura was injected but not ulcerated. On section the usual bony architecture was found to be replaced by gray tumor tissue.

In the other organs the changes were mainly those of senescence and arteriosclerosis. The heart was small, the lungs emphysematous, with a few patches of focal pneumonia, and the kidneys mildly scarred. The pancreas was largely replaced by fat tissue; the spleen was tiny. The endocrine glands were not remarkable. The brain was atrophic and showed scattered patches of encephalomalacia. The calvarium was thick-walled and sclerotic; the tables were indistinct.
Microscopic Findings: Atrophy of the heart and spleen, emphysema and focal pneumonia in the lungs, slight scarring of the kidneys, and extensive lipomatosis of the pancreas corroborated the gross findings. The liver showed atrophy of the cell cords, congestion of the sinusoids, and pressure necrosis. The bones of the calvarium were dense and sclerotic. The essential brain findings were: disappearance of many ganglion cells, Alzheimer cell changes, and senile plaques.

Of the adnexa, the left were not noteworthy. The right ovary showed atrophic ovarian tissue compressed by carcinoma. The uterus and vagina were atrophic, and the latter covered by a thin epithelium.

Several sections of the senile warts in various stages revealed the well-known typical structure. The lesions nowhere extended below the epidermis and nowhere showed active proliferation.

The papules in the left groin were covered by atrophic but intact epithelium. In the deeper portion of the corium lay some irregular, relatively acellular scirrhouss carcinoma.

The small tumor mass in the vulva was removed in toto. Serial sections through several parts differed but little. In cross-section the mass was roughly wedge-shaped with its base towards the surface and merged gradually at its margins with the neighboring "eczematous" epidermis; it was sharply demarcated from the subjacent subcutaneous adipose.

Most of the preparations were Zenker-fixed, and stained with hematoxylin-eosin. A few special stains were used.
tissue. Over the main mass, to be described later, the epithelium was reduced to a flattened band, two or three cells deep, with moderate hyperkeratosis and parakeratosis (Fig. 1). The basal-cell layer was thin; the papillae were absent or very short. The general impression was unmistakably that of severe compression by the subjacent carcinoma. Occasionally there was visible in this epidermis a "Paget cell" and, in a few focal areas, intraepithelial masses of cells, resembling and continuous with the underlying tumor (Fig. 2). As the periphery of the wedge was approached, the epidermis became broader and assumed a Paget character of wide quantitative variability.

The epidermis varied in thickness, but in general was thickest, and its papillae were most

**FIG. 3**  **FIG. 4**

**FIG. 3. EARLY INVASION OF EPIDERMIS BY "PAGET CELLS," SHOWING PREDOMINANCE IN BASAL LAYERS AND DISCONTINUITY OF INDIVIDUAL CELLS. × 260**

**FIG. 4. EPIDERMIS: PAGET'S DISEASE OF THE SKIN**

The "Paget cell" (A), with clear borders, is pushing aside and is discrete from the epidermal cell proper. The neighboring epidermal cells are compressed by the "Paget cells" (B). C = basal-cell layer. × 450.

striking, where "Paget cells" were most abundant. It appeared that invasion occurred from below, i.e., travelling from the basal-cell layer towards the surface, for when only a few "Paget cells" were present, they tended to localize in the basal-cell layer (Figs. 3 and 4). The more superficial layers, as a rule, were invaded only when the process became more extensive. The cells were scattered singly, or in small or large groups, and were frequently discontinuous (Figs. 3 and 4), as shown in serial section. Wherever they appeared the neighboring epidermal cells were displaced and compressed, with only parallel thin rows of intercellular bridges, telltale of the flattened cells (Fig. 4). The "Paget cells" were usually clearly discrete (Fig. 4) and appeared to push aside the epidermal cells with which they were not intimately related. Their boundaries were usually distinct and it was not possible to demonstrate intercellular bridges, nor could anything else suggestive of a transition between the epidermal and "Paget cells" be demonstrated. Focussing at various levels only corroborated the impression of discreetness.

The "Paget cells" were highly pleomorphic. When isolated, such a cell generally appeared large, round or oval, frequently as if swollen, with a pale pink-staining delicately granular or lacy cytoplasm and a large, round, vesicular or often hyperchromatic nucleus (Figs. 3 and 5). Not uncommonly, although the cellular outline remained intact, consid-
FIG. 5. EPIDERMIS: PAGET'S DISEASE OF THE SKIN
This stage is midway between Fig. 3 and Fig. 8.  × 375.

FIG. 6. EPIDERMIS: HYPERKERATOSIS WITH "PAGET CELLS" (A) CARRIED OFF IN THE DESQUAMATING LAYER
These were the "psorosperms" of Darier, always found in the scrapings of the affected skin, and were presumably pathognomonic. Note also tendency of "Paget cells" to be surrounded by spaces, (B), as if secreting.  × 200.
erable portions of cytoplasm seemed to have fallen out. Most of the “Paget cells,” however, were not of this type but were elongated or fusiform and often quite irregular in shape. The corresponding nuclei were indented, either vesicular or hyperchromatic and occasionally pyknotic. Bizarre shapes were common. Curious elongated or pointed cytoplasmic projections seemed sometimes to enter, wedge-like, between two epidermal cells. Such findings were reminiscent of pseudopodial movement. The presence of all these cells —irregular in shape, size, and appearance—resulted in a rich morphological variety.

Often the cells lay loosely, disconnected or united by long, thin, filamentous processes. The spaces of the resultant meshwork contained a thin, granular débris, suggestive of watery secretion. Similar spaces were common between the dermis and the basal-cell layer when the latter contained significant numbers of “Paget cells” (Fig. 6). Groups of columnar

![Image](image_url)

**Fig. 7. Epidermis: Paget’s Disease of the Skin: Group of Cuboidal Cells Arranged in Small Acinus (A)
B = epidermis. × 250.**

cells with basally placed nuclei were often arranged around such spaces in a suggestive tubular or acinar (Fig. 7) formation.

No keratinization of the “Paget cells” was demonstrable, as was beautifully seen in the round spaces with pyknotic nuclei carried towards the surface in the desquamating cornified epidermal layer (Fig. 6). The apparent invasiveness of the “Paget cells” and the varying signs of activity made it difficult to believe that they were the result of dyskeratotic or degenerative phenomena. Further evidence of vigor and growth was seen in the cores of capillary-rich connective tissue (well brought out in the Mallory connective-tissue stain) which extended up from the dermis into the epidermis, roughly proportional in amount to the degree of epidermal involvement. No downward growth of the epidermis into the corium was evident, although, as will be described presently, the reverse was not rare.

The dermis beneath the affected epidermis was composed of a dense collagenous fibrous framework in which new-formed capillaries and inflammatory cells were prominent (Fig. 8). The degree of involvement of any area of dermis and its corresponding epidermis seemed roughly proportional. The infiltrating cells were mainly lymphocytes, but plasma cells were
also present. Occasional large mononuclear cells, rare polymorphonuclear leukocytes, and, infrequently, eosinophilic myelocytes were found.

The carcinoma proper varied in appearance, even in its presumably original site. The major portion, especially in the deeper layers, was composed of long cords of double-rowed cells, separated by strands of dense collagenous tissue and having definite or suggested lumina. The individual cells were not unusually variable in size and tended to be cuboidal or polygonal. The nuclei were vesicular and hyperchromatic. The cytoplasm was pale and finely vacuolated, but with occasional large vacuoles. In the more superficial portions,

![Image](image.png)

**Fig. 8. Full-Blooded Classical Paget's Disease of the Skin**

The dermis shows fibroblastic proliferation, increase in the number of capillaries, and small-round-cell infiltration. × 150.

near the compressed epidermis, the connective tissue grew less prominently and the carcinoma cells tended to grow in sheets which invaded and enormously distended the lymphatics (Fig. 1). Such groups of cells extended at times directly into the epidermis and these intraepidermal "Paget cells" were indistinguishable from the underlying cancer cells (Fig. 2). The latter were large, pale, and granular with small and large vacuoles. There was an apparent tendency towards arrangement in ducts and acini. The vacuoles of the cells and the acinar spaces contained varying amounts of granular débris, suggestive of a secretory process (Fig. 1).

Numerous large sweat glands and ducts lay in the deeper portion of the dermis. Most
of these were not remarkable but not infrequently "Paget cells" nestled in the presumably normal, finely vacuolated sudoriparous epithelium. Here and there groups of glands and ducts with widely dilated lumina and flat epithelium pointed to obstruction of the ducts, presumably by carcinoma. A few ducts with metaplastic epithelium were found. Of greatest interest, however, were numerous foci in which groups of sweat glands were intimately mingled with masses of cancer cells (Fig. 9). The latter were vacuolated and arranged somewhat crudely in acini, as if mimicking the former. Not uncommonly it was difficult to be certain whether an individual acinus was normal sweat gland or carcinoma.

Fig. 9. Periphery of Main Tumor Nodule: Group of Sweat Glands and Ducts (A) Intermingled with Glandular Carcinoma

It is frequently difficult to be certain which acini are "normal." B = similar but scirrhous carcinoma. × 90.

Histologically the various metastases duplicated almost every feature of the primary carcinoma and of the intraepidermal "Paget cells." The varying proportions accounted for the apparent diversity in appearance. Most of the carcinoma grew in long cords, invaded lymphatics, and so stimulated connective-tissue proliferation as to be definitely scirrhous. It was interesting to note, in many of the metastases, a dense lymphocytic infiltration in the connective tissue bordering on the carcinoma. This cellular reaction to the carcinoma was in no way distinguishable from the similarly involved dermis of the "pagetized" skin, a reaction considered highly characteristic of this affection. Distinct as well as abortive acinar and tubular structures, containing pink-staining granular debris, were found everywhere (Fig. 10). In the adrenal metastasis, acini, as well as intracellular vacuoles, were abundantly filled with a thin, homogeneous, pale bluish-staining material. Another familiar pattern present in almost all the metastases was the peculiar loose meshwork formed by the long filamentous processes noted above as common in the skin. Typical "Paget cells," i.e. large round cells with pale, vacuolated cytoplasm, although scattered throughout, were especially prominent in the metastatic rib lesion (Fig. 11).

It is of interest to note that only a few mitotic figures were found in the many sections
studied. This is consistent with the clinical history of slow growth, which obviously enough had but little influence on the malignant invasiveness of the tumor. The mode of extension was mainly intralymphatic.

**Review of Extramammary Paget's Disease**

The first suggestion of an extramammary location was purely clinical and was made by Paget himself in his original classic description (1). He wrote: "I believe that a nearly similar sequence of events may be observed in other parts. I have seen a persistent 'rawness' of the glans penis like a long-enduring balanitis, followed after more than a year's duration by cancer of the substance of the gland."

![Figure 10](image)

**FIG. 10. Representative Field in Rib Metastasis**

Note tendency towards formation of acini (A) by cuboidal cells. Pink-staining debris present in many of the acinar spaces (B). X 25.

The next case, frequently referred to, is that of Morris (6) recorded in 1880. The patient was a woman of sixty who nine years previously had discovered a patch of eczema on the right side of her neck. The lesion was twice excised but recurred, eventually in the form of a hard ulcer. Morris stated that "the antecedent skin disease . . . consisted of the desquamation of thin, light scales from a slightly reddened but otherwise unaltered surface." No further details were recorded and no mention was made of microscopic study. Morris' diagnosis was epithelioma, not Paget's disease, although he compared it to the latter. From the data, a diagnosis of superficial epithelioma or possibly Bowen's disease appears most plausible.

In 1889 Radcliffe Crocker (7) presented the first clear-cut case of Paget's disease in an extramammary site. His patient, a male aged sixty, had first observed a small ulcerated zone at the root of the penis three years pre-
viously. The lesion proved intractable to therapy and spread gradually to involve the entire left side of the penis and scrotum (Crockier’s report has a beautiful colored lithograph of the lesion). Two small nodules were found in the center of the ulcerated area. The excellent detailed gross and microscopic descriptions are characteristic of Paget’s disease. The nodules were composed of cancer cells, alveolar in type. Crocker concluded that “it is certainly not an epithelioma in the ordinary sense, for it is clearly not derived from the epidermis . . . and there are strong grounds, moreover, for believing that the malignant change starts from the sweat- and sebaceous glands. . . .”

A much quoted case was reported by Tarnovsky (8) in 1891 at the Fourth Congress of Russian Doctors. The entire abstract (trans. from the French) follows: “He has actually under treatment a patient with psorospermosis of the penis, wholly comparable to Paget’s disease. Because the patient is syphilitic, the disease is thought to be of specific etiology. In addition to the pain experienced by the patient, there is induration and ulceration, but no cancer.” The data are obviously insufficient and the case must be rejected.

In 1893 Darier, the propounder of the then commonly accepted psorosperm theory, reported with Couillaud (9) a case in a man of seventy-two, who for fifteen years had had a lesion resembling Paget’s disease. This began at the anus and, resistant to all therapy, gradually spread to involve the entire perineum, including the scrotum, buttocks, and coccyx. The clear clinical description and the biopsy report leave no doubt that this was a genuine case of Paget’s disease. The relation to cancer was mentioned but casually: “we have not yet noted, to date, any trace of cancerous nodules.” No follow-up was recorded.

Tommasoli (10) in 1893 reported the long clinical history of a sixty-six-
year-old patient whose illness began in 1888 with pruritus of the glans penis and induration of the prepuce. The indurated area was red and exquisitely painful, and the entire region became involved. Superficial ulcerations appeared on the glans. A dorsal slit was eventually necessary. In 1890 the thick, indurated prepuce was removed. The wound healed expect at the site where ulceration occurred. Small red nodules appeared in the depth of the ulcer. In 1891 the penis was amputated at the base. In 1892 the carcinoma recurred in the stump, spread gradually "into the scrotum and subcutaneous tissue of adjacent regions," and the patient died from "acute uremia." The removed prepuce was said to show "an incipient epithelioma," which is the sole histological observation. No description of the skin nor of the carcinoma was given. Although the clinical features are consistent with the diagnosis of Paget's disease, no definite proof is at hand.

A brief abstract of a case presented by Pick (11) appeared in 1891. The patient had a weeping eczema of the glans penis of eighteen months' duration. Excision was followed by temporary cure, then by a recurrence, associated with small nodules. The recorded findings were "abundant number of psorosperms" in the epidermis, small round-cell infiltration beneath and nearby "the typical picture of a cancerous growth." Though the case was probably one of Paget's disease with cancer, an absolute diagnosis is not warranted.

Ravogli (12) in 1894 described an "aged lady" with Paget's disease of the nose. The process began at the inner canthus of the right eye and suggested superficial epithelioma. Histologically there were "hypertrophy of . . . epidermic cells" and inflammatory reaction "among the papillae and glands of the skin." By scraping the surface "large, peculiar cells . . . oval . . . with double contour" were found which "in specimens prepared in glycerine . . . showed ameboid movements." The latter, in accordance with the then dominant psorosperm theory, were responsible for the diagnosis of Paget's disease. The clinical description and histologic data, however, are insufficient for such a diagnosis. In 1910, Ravogli in the discussion of Hartzell's paper (13) stated that his patient had died several years later with carcinoma which spread to the cervical glands.

In 1896 Winfield (14) presented to the Brooklyn Dermatological Society a patient with a four-year-old eczema-like eruption of the lower lip at the mucocutaneous border. This was excised and was microscopically an epithelioma. The patient died in a year with node involvement (Hartzell, 13; discussion by Winfield). Except for a superficial clinical resemblance, the data do not justify a diagnosis of Paget's disease.

Sheild's patient (15), reported in 1897, was a male aged sixty with a spreading eczema of eight years' duration, involving the root of the penis and scrotum and resistant to therapy. In the lesion were three small tumors varying in size from a "large walnut to a hazelnut." The inguinal nodes were unaffected. During the same year Rolleston and Hunt (16) published a careful microscopic study of Sheild's case. The epidermal changes, which are accurately described, extended into the sweat and sebaceous glands and were typical of Paget's disease. The nodules were carcinomatous and invaded the deeper layer of the dermis. The masses of epithelial cells resembled "the coccidia described by Darier and Wickham. . . . There is nowhere any
keratinization or corneous change.” The structure was alveolar and “the alveoli are surrounded by the plasmoma cells seen in the superficial layer of the dermis.” These and other interesting observations led Rolleston and Hunt to consider the source of the cancer to be either the sweat or sebaceous glands, probably the latter. Obviously a case of Paget’s disease, this case is interesting in that it was associated with a definite adenocarcinoma, with evidence suggesting a relationship to the skin glands.

Dubreuilh (17), in 1901, reported the first case observed in the *vulva*. The patient, aged fifty-one, had developed an itchy, slightly painful red papule near the clitoris, three years previously. This proved resistant to therapy and at the time of examination involved “the anterior third of the left labium majus, the anterior fourth of the right labium majus, the clitoris, vestibule and urethral orifice.” An indurated enlarged node was present in the left groin. The entire mass was removed surgically; there was no recurrence one year later. The clinical and histological features are those of classical Paget’s disease. Dubreuilh stated that “in some parts of the nymphae deep epithelial masses were found” and in a few places he casually mentioned acini. He described invasion of the sweat glands and hair follicles by “Paget cells” but did not attempt any correlation. He believed the skin disease to be a superficial form of cancer. It was probably an adenocarcinoma.

A brief report by Holzknecht (18) of a case in the *axilla* appeared in 1903. The patient was a woman with a lesion “of twelve years’ duration, in the beginning in the form of an eczema, then changing to a flat, relatively benign epithelial malignancy with the characteristic individual cells, and the definitive structure of deep-lying carcinomatous masses (here in the form of an adenocarcinoma) with metastases and cachexia.” No further data were presented and, although the diagnosis of carcinoma (“alveolarkrebs”) appears definite, the diagnosis of Paget’s disease, while probable, cannot be confirmed.

Matzenauer (19) presented in the same year a man, aged forty-four, from whose *nose* Kaposi had removed a hornified squamous-cell carcinoma five years previously. The surface of the nose subsequently became red and eczematoid. No further clinical features and no histologic description are offered in the brief report. Although with the evidence at hand one cannot rule out invasion of the skin by cancer, this case must be considered as squamous-cell carcinoma with recurrence.

The next case, reported by Jungmann and Pollitzer (20) in 1904, is difficult to evaluate. A woman, aged forty-six, had a lentil-sized, red, moist nodule in the *axilla* thirteen years previously. Despite treatment the lesion had gradually spread to involve the breast, arm, and back. At the time of examination a “fig-sized tumor” was present in the center of the lesion and was fixed to the underlying tissue. This had appeared several months earlier. Extensive x-ray therapy healed the skin but the underlying tumor was unaffected. A year later biopsies were taken from the skin and tumor. The histological description and the few accompanying illustrations, though consistent with a diagnosis of Paget’s disease, are not unequivocal. The tumor nodule was composed of anastomosing columns or broad nests of cells, which at the margins were clearly composed of cuboidal or columnar epithelium, suggesting basal-cell epithelium. There were also present structures which the authors
considered might be mistaken for "gland lumina." With the data at hand, this case is best considered as probable Paget's disease associated with "non-keratinizing" carcinoma, possibly basal-cell, possibly glandular in type.

Fox and Macleod (21) recorded the first umbilical localization in 1904. Their patient, a male aged sixty-five, had had a patch of eczema over the umbilicus for eleven years. This remained intractable to therapy. No carcinoma was found. The microscopic description of the biopsy findings, as well as the clear accompanying illustration, are much more consistent with what is now called Bowen's disease than with Paget's disease.

The first unequivocal case of Paget's disease in the axilla was recorded by Zieler (22) in 1904. A woman aged forty-two had a typical lesion in the left axilla. Swelling and pruritus had ushered in the disease five years previously. Histological examination showed Paget's disease. The entire lesion was excised but the following year the patient returned with a recurrence extending towards the breast and back, and adherent to the firm underlying lymph nodes. She disappeared from clinical observation but later that year died from extensive pulmonary tuberculosis. Zieler's histological description is definitely that of Paget's disease associated with underlying carcinoma, which in the lymph nodes was tubulo-acinar in structure. Zieler himself, who was of the opinion that mammary Paget's disease always arises in the milkducts, by analogy considered a possible sweat gland origin in this case.

In 1905 Sequeira (23) presented to the London Dermatological Society a seventy-seven-year-old male with a painful red patch at the junction of the prepuce and glans penis, present for two years. Circumcision was followed several months later by the appearance of a red, raw area in the sulcus. There was no infiltration and the lymph nodes were unaffected. In 1912, in the discussion of Milligan’s paper (24), Sequeira mentioned the above case (presumably), saying that a nodule of carcinoma later developed in the bulbous urethra. The absence of histologic or further clinical and pathologic data renders unreliable both the diagnosis of Paget's disease and carcinoma.

In 1905 Fordyce (25a) reported a case, already reported clinically by him (25b) in 1903. A woman, aged sixty, had received an injury in the left gluteal region seven years previously. One year later at the site of the injury a red spot appeared and increased to a diameter of 3 inches. Intensive x-ray therapy was effective and one year later only a scar remained. Nowhere in the histologic description were "Paget cells" described. The accompanying illustrations—especially his Fig. 3—show what appears to be a basal-cell tumor, a diagnosis readily compatible with the findings. As a matter of fact, Fordyce later retracted the diagnosis of Paget's disease (see Discussion of Hartzell's case, 13).

Rosenberg (26) reported in 1909 the second case arising in the vulva. The patient, aged seventy, had a red itching spot on the left labium majus four years previously. The lesion spread to involve both labia majora and minora, clitoris, perineum, and buttocks. The left labium majus was infiltrated and showed two small ulcers. The detailed clinical and histological descriptions—with clear photomicrographs—are undoubtedly those of Paget's disease. The photomicrograph of the ulcer shows carcinoma in the lymphatics of the dermis, and similar masses of cells were found in the subcutaneous
tissue. These cell masses are illustrated with insufficient magnification to permit more accurate analysis of the structure. Rosenberg did not characterize them, saying only that "intercellular material was completely lacking."

Hartzell (13), in 1910, stated that he had examined microscopically two of Dr. Charles N. Davis' cases of Paget's disease—one of the glans penis, one of the scrotum. No corroborative data of any sort were offered.

Hartzell (13) also described a case which he saw in Duhring's clinic. The lesion involved the "entire region lying between the tuberosities of the ischia, the tip of the coccyx above and the perineum below... In the center of the right half of the diseased region was a small button-like elevated lesion presenting the external features of an epithelioma." Clear as the clinical features were of both Paget's disease and carcinoma, the absence of any microscopic data forces us to dismiss both.

Hartzell's (13) own case involving the forearm is of interest. A man aged sixty-four had an extensive patch of Paget-like eczema on the outer side of the left arm, below the elbow. Numerous small nodules and an infiltrated superficial ulcer were found in the involved area. The history stated that fifteen years earlier a much traumatized pigmented mole began to spread and was eventually lost in the progressive ulceration. Histologically, the corium was replaced by large round vacuolated cells with "histological features characteristic of a naevo-carcinoma." The epidermis, judging by the illustration, was invaded by masses of vacuolated cells similar in character to those in the dermis, and indeed not unlike the picture in Paget's disease. The cellular structure ordinarily observed in the latter, however, is not seen nor mentioned in the brief description of the epidermis; the invasion was rather by sheets of cells. Similar epidermal invasion by masses of nevus cells is a well-known characteristic of nevo-carcinoma (Cf. Dawson 27). This case, then, is best viewed as a nevocarcinoma with intraepidermal spread, simulating Paget's disease.

Winfield, in the discussion of the above case, recalled that he had seen a woman with a somewhat similar history. For eight years she had had a peculiar raw, red area "typical of Paget's disease of the nipple" over a portion of the scapula irritated by a corset. This lesion and a large congenital pigmented mole on the breast were removed simultaneously. Histologically, "the patch over the scapula gave the typical picture of Paget's disease and the mole also showed the same histological appearance." It is obvious that the nature of the lesion must remain speculative.

Another questionable case is Milligan's (24), presented in 1911. There is no record of a biopsy. The scanty clinical report states that the patient, a woman aged thirty-one, had an ill-smelling discharge from the umbilicus which commenced four years previously, with redness on the right side. Radium treatment cleared the lesion, apparently completely.

Towle's (28) case, reported in 1912, was probably not Paget's disease. In any event, the material is insufficient for definite diagnosis. His patient, a man aged seventy-four, had had for twenty-five years a large, red, raw interscapular lesion in the center of which there developed a projecting mulberry tumor. "A histological section made from the outer border of the infiltrated area through to the lobulated tumor revealed an epitheliomatous
condition of the tumor and the skin immediately adjacent, but in the tissue more distant only a process suggesting a chronic inflammation without true epitheliomatous degeneration." "Paget cells" were not even mentioned.

Polland (29) in 1914 published the case of a woman, aged sixty-one, who two years previously developed a lesion on the right cheek directly beneath the eye. The corresponding submaxillary glands were large and firm. Histologic section showed epidermic carcinoma but "Paget cells" were "nowhere seen definitely." It is difficult to see why this case was recorded as Paget's disease.

In 1914 there appeared an abstract of a Russian report by Grinchar (30). The patient, aged fifty-five, developed pruritus of the vulva four years previously. This was followed by the appearance of papules on the right labium majus. In two years a typical, malignant, parchment-like indurated area formed and soon crusted. The abstractor stated that "Grinchar, like Hartzell and others, is of the opinion that careful microscopical observations would show that cancer in such cases had existed from the outset." Histologic data, however, were not recorded, and suggestive as this case is of both Paget's disease and carcinoma, it cannot be accepted.

Ormsby's (31) case, reported in 1915, had neither a clinical work-up nor a histologic study. The patient, aged fifty-seven, had "superficial epitheliomatosis resembling Paget's disease" for thirteen years. The description, however, appears to be rather against a diagnosis of Paget's disease. There were 12 patches over the back. These varied from half an inch to several inches in diameter, were bluish-red, covered with scales, and showed a well defined margin with a pearly border.

Potter's (32) case, presented briefly in 1915, was in a woman aged forty-seven, who had "a pedunculated fibrous teat, which she called a wart" (location not stated). This had fallen off five years previously and a red, sore area had appeared at the site. "The microscopical findings showed a dyskeratosis with the involvement of both the prickle-cell layer and basal-cell layer. . . . There were no psorosperm-like bodies present. . . ." The data are obviously inadequate for a diagnosis. In the discussion of the case at the time of its presentation Drs. Trimble, Wise and Jackson were of the opinion that the lesion represented a basal-cell epithelioma.

In an extended report in 1917 Sekiguchi (33) recorded a case involving the scrotum and also referred, by name only, to a case of Pospeloff involving the prepuce and fraenum, to one of Kren involving the vulva, and to one of Belot involving the back. No further details were given nor could references be found to the three cases to which reference was made. Sekiguchi's own patient, aged sixty-five, had had eczema of the scrotum for nine years. Pruritus was severe; the lesion eventually eroded and spread over the entire right scrotum and root of the penis. A crater-shaped indurated ulcer was located in the center of the involved area. The inguinal lymph nodes were shotty; the right leg was edematous. The penis, scrotum, and inguinal nodes were excised in toto. The indurated ulcer was composed of cuboidal and columnar cancer cells which "must be classified as an adenocarcinoma." The neighboring skin showed Paget's disease and "many 'Paget cells' were found in direct transition from glandular cancer cells." The carcinoma extended
deep into the subcutaneous tissue; the inguinal nodes showed glandular carcinoma. Sekiguchi's description and clear photomicrographs are sufficient to designate this as unequivocal Paget's disease and adenocarcinoma. The unilateral edema suggests that invasion of the pelvis had already occurred, although Sekiguchi did not mention the further course of the patient. He was inclined to consider a sudoriparous origin for the tumor and compared the sweat glands to the mammary glands—Paget's disease being either cancer of the sweat glands or of the lactiferous ducts.

Stelwagon's (34) case involving the nose may be dismissed. The entire report consists of a single sentence. "I have met with a case somewhat similar to Ravogli's case, in a woman aged sixty, the whole nose being superficially involved and eroded and clinically suggestive of this malady."

Satani (35) in 1920 reported a case in a man aged seventy-four, with (presumably) incidental penile condylomata. He had always had a pea-sized wart in the right axilla. Six years previously it began to enlarge, became red, itching, and moist, and remaining resistant to all therapy eventually reached a diameter of 7 cm. In the center of the mass was a nipple-like nodular tumor. The axillary and supraclavicular nodes were not enlarged. The entire patch was removed and the histological description is that of Paget's disease and carcinoma. The details as to the carcinoma are insufficient for the establishment of the type, although adenocarcinoma seems most likely. Thus, although the author claimed to have seen "two or three corneous pearls" he also casually mentioned elsewhere that the cells were placed "more in a columnar manner" and again that there were "groups of proliferated big Paget cells producing distinct alveolation." The photomicrographs are not sufficiently clear to be of use in the diagnosis.

Trimble's (36) case, presented in 1923, was that of a woman aged sixty-three, who thirty years previously developed a dusky red lesion to the right of the umbilicus. The lesion finally involved the entire right lower quadrant. No further details were recorded, although during the discussion Trimble stated that the lesion was a basal-cell epithelioma but some keratotic bodies led him to put it into the Paget group. Obviously a diagnosis of Paget's disease is questionable.

Boot's (37) case of Paget's disease of the nose, listed in some series (40), was reported in 1923. Eponymic confusion was apparently responsible for the inclusion of this obvious case of Paget's disease of bone.

Arzt and Kren's (38) case reported in 1925 is undoubtedly a case of Paget's disease of the vulva. The patient was a seventy-year-old woman with symptoms of several months' duration. The entire right labium majus was thickened and was clinically characteristic of Paget's disease. "Paget cells" were present, mainly in the basal-cell layers. Although Arzt and Kren considered this as precancerous, in the absence of further studies or follow-up underlying carcinoma cannot be ruled out.

An undoubted case of Paget's disease of the vulva, associated with carcinoma, was reported in 1927 by van der Hoop, Bonne and Wassink (39). Their patient, aged forty-three, had had psoriasis since childhood. A painful eczema, followed by ulceration, appeared on the right labium minus in 1922. Therapy, including x-ray irradiation, was unavailing. Four months prior to
admission the patient had noticed a lump in the right labium which grew steadily larger. The entire vulva was excised in September 1926 and recovery was uneventful. The histological examination showed the typical features of Paget's disease and extensive carcinomatous infiltration of the underlying tissue. The carcinoma was alveolar in type and strongly suggested a sweat gland origin to the authors (see their Figs. 4 and 8). They also noted "that in the Paget epithelium there were isolated areas of carcinoma with a tendency toward duct structure." The carefully prepared histological and photomicrographic material amply confirms the diagnosis of Paget's disease and adenocarcinoma.

Susman's (40) case, reported in 1928, in a male aged sixty, is equivocal. An itching excoriation at the glans penis of a year's duration was followed by a sharply margined red eczematous area. The penis was amputated. No deep carcinoma was found and there was no recurrence three months post-operatively. Although the gross illustration is suggestive of Paget's disease, a drawing of a microscopic field shows a fairly characteristic basal-cell tumor invading the dermis, and indeed the author himself "would stress the general similarity of the histology of this lesion to that of basal-cell carcinoma." Another drawing of a small epidermal rete peg under higher magnification, although showing small and large clear cells scattered irregularly through the epidermal cells, is not convincing evidence of Paget's disease.

In 1928 Tashiro (41) reported a case in which the vulva was involved. The patient, aged thirty-three, had a flat, itching, slowly progressive lesion for three years in the region of the left labium minus and commissure. The entire area was excised. In the basal layer of the epidermis there were many single "Paget cells" with which were associated the other typical findings of Paget's disease. This is a clear case of the disease, and the accompanying photomicrographs are corroborative. The presence of carcinoma and the further clinical course were not discussed.

Civatte's (42) case in the axilla was reported in 1928. His patient, a woman aged sixty-seven, suffered a spontaneous fracture of the right radius. She had also at the time a deep, crater-like lesion involving the entire left axilla. This had presumably appeared ten years previously with a slowly spreading patch of eczema which did not yield to therapy. The overlying skin remained supple, however, and no underlying nodules were felt until eight months previously. These became rapidly ulcerated and gradually involved the entire eczematous patch in an indurated mass. Careful examination of the left breast was negative, nor could any relevant history be elicited. X-rays showed a decalcified zone in the second lumbar vertebra and the patient complained of lumbar pain. She was given a course of x-ray irradiation with almost complete healing of the axillary wound, but several weeks later new bony metastases developed and death ensued. No post-mortem findings were recorded but two biopsies had been taken. Study of these showed Paget's disease of the skin and an underlying glandular cancer extending into the subcutaneous tissue. The carcinoma was unmistakably of sweat gland origin. Civatte's drawings (his Figs. 4, 5, 6), showing epithelial transitions in the sweat glands, are unusually striking. That we are dealing here with Paget's disease of the skin and sweat gland carcinoma seems quite clear.
Miescher's (43) case was recorded in abstract in 1929, and although both Paget's disease and carcinoma were apparently present, the briefness of the report precludes certainty. The data are limited to the following: "female, seventy-four, pale red spot, eroded at upper pole, dull red papules and, down to femoral region, several hard intracutaneous metastases the size of a pin head. Histologically: loosening of epidermal cell elements, hydropic degeneration and building of cell masses. Extensive invasion of lymph channels by cells."

Petges, Muratet and Lecoulant's (44) case, also reported in 1929, is difficult to interpret because of the complications. Following a kick in the vulva in 1925, there developed an ulcerated, flat, bright red, slightly projecting, sharply marginated, non-indurated lesion on the right side near the prepuce of the clitoris. At that time (1927) the patient's blood Wassermann was strongly positive and the palpable inguinal nodes were considered part of a syphilitic process. Histological examination of the vulvar lesion showed "particularly in the deformed hyperplastic Malpighian layer numerous vacoulated, some multinucleated cells with absent intercellular bridges and more numerous towards the basal layer." With diathermy-coagulation the lesion cleared and only a scar remained. Shortly thereafter the patient returned with a recurrence on the border of the scar. The authors promised to study the recurrence histologically. Since no illustrations and no further details were offered, this case, although probably Paget's disease, cannot be definitely accepted. Carcinoma was not mentioned.

Yoshida (45) reported three cases of localization in the penis in 1929. One patient, aged fifty-four, developed a small eruption at the coronary sulcus "which grew in fourteen years to size of a thumbnail . . . burning and tingling. . . . Roentgen ray and radium had no effect; amputation of the penis was performed. Histological examination showed the typical features of Paget's disease, such as epidermal hypertrophy, epithelial edema, proliferating downgrowth of the rete pegs into the corium, the presence of 'Paget cells' and a cellular infiltration in the corium."

The second and third patients were aged fifty-four and thirty-four, and the course of the disease four and fourteen years. "The site of the lesion in both cases was the sulcus coronarius. By clinical and histological examination the diagnosis of Paget's disease was confirmed in the two cases, for both of which the excision of the lesion was performed with great success." This is the report in its entirety, and however suggestive, is insufficient for critical analysis.

Drake and Whitfield's (46) case, reported in 1929, occurred in a woman, aged sixty-eight, who had been having soreness and pruritus of the vulva for eight years. Gradually the entire vulva and perineum were involved. On account of the extent of the lesion, only a biopsy was performed. The gross description (there is a beautiful colored drawing) is characteristic enough, and the accompanying histologic descriptions and photomicrographs occasion little hesitation in accepting this as a case of genuine Paget's disease. The authors noted extensive involvement of the sweat glands but "no apparent attempt . . . to grow beyond . . . the limiting membrane of the duct or gland . . . though the tubules of the latter are here and there stuffed with
cells." Clinically the authors observed enlargement of the inguinal nodes but also stated that "there is no massive tumour in the depth."

In 1930 Susman (47) reported another case involving the penis. This was in a man aged sixty-six, with a six-year-old red, raw, glazed lesion of the glans penis. "There was no sign of cancer in the body of the penis." The lesion resisted all treatment. The patient died suddenly a few months later. In the absence of further clinical history, biopsy or post-mortem findings, the diagnosis remains merely a clinical impression.

Da Costa (48) in his textbook of surgery casually mentioned that he had seen two cases of Paget's disease of the penis, but gave no further details.

Busman and Woodburne's (49) case, reported in 1931, was probably a superficial carcinoma of the Bowen type rather than Paget's disease. A negro, aged forty-six, had for three years had an ulcerated lesion on the glans penis. The biopsy showed "epidermoid carcinoma" but no pearl formation, although the authors state that "keratinizing" was seen in individual cells. X-ray therapy was effectual and there was no recurrence fourteen months later. Neither the description of the gross nor of the microscopic appearance is consistent with Paget's disease. The accompanying photomicrographs with their large bizarre cells (see especially the giant cell in the authors' Fig. 1) are suggestive of Bowen's disease.

Glass (50) reported a case on the vulva in 1933. From the brief data presented, it would be difficult to label this definitely as Paget's disease. His patient, aged seventy-six, complained of pruritus vulvae and prolapse of the uterus; the duration of neither was stated. The only findings on examination were cervical polyps; a high perineorrhaphy was done. The pruritus grew worse and the vulva became red. Six months later several firm areas on the left labium were diagnosed as leukoplakia. Total vulvectomy was performed; there was no recurrence several months after this. Neither the descriptions nor the accompanying illustrations furnish convincing evidence of Paget's disease. Carcinoma was nowhere mentioned.

Louste and Rabut's (51) case, reported in 1934, occurred in a man of sixty. Redness and pruritus of the right nipple developed fifteen years previously. Shortly thereafter a similar lesion appeared over the right scapula. Both lesions spread. The gross description is consistent with Paget's disease in both sites. Histologic preparations of both were studied and besides Paget's disease showed carcinoma, which was "polymorphous"—now "spinocellular," now "basocellular," now "sweat gland" in type. The authors concluded that the extramammary lesion was "Paget's epithelioma of sweat gland origin, but very polymorphous." No illustrations are given and the histologic descriptions are largely interpretive, so that it is difficult to be certain of either diagnosis.

The most recent report of a case involving the vulva was Dörffel and Grimm's (52) in 1935. Their patient, aged eighty-two, had had an itching lesion in the left groin for two years. This spread to the right groin and then to the lower abdomen. The gross and microscopic illustrations and the biopsy report are all typical of Paget's disease. The authors found no clinical evidence of carcinoma.

Noguer-More's (53) case, reported in 1935, however suspicious, must be
rejected on account of insufficient data. His patient, aged sixty, had a severe pruritus at the base of the penis and crotch. This progressed to an alternately dry and wet ulceration which spread to involve the entire scrotum and base of the penis. The border of the lesion was sharp and its gross appearance—adequately described and illustrated—was typical. The histologic appearance of several "fragments" is presented briefly and without illustrations—and though the condition was probably Paget's disease, judgment must be guarded. The author failed to note carcinoma, but the latter can hardly be considered as ruled out by the examination of a few "fragments."

To summarize the above, it is evident that the majority of the 58 cases must be discounted completely. About 10 are probably Paget's disease but with insufficient published evidence. In only 15 is a definite diagnosis of extramammary Paget's disease warranted—4 in the male genitals (Crocker; Darier and Couillaud; Sheild and Rolleston-Hunt; Sekiguchi); 8 in the vulva (Dubreuilh; Rosenberg; Arzt and Kren; van der Hoop, Bonne and Wassink; Tashiro; Drake and Whitfield; Dörffel and Grimm; Weiner); and 3 in the axilla (Zieler; Satani; Civatte).

**Nature of Paget's Disease**

The nature of Paget's disease is still a matter of considerable dispute, although no longer do the more active students of the disease diverge on its relation to cancer. No instance has been uncovered, to our knowledge, indisputably unrelated to cancer. On the other hand, the number of instances reported following, preceding, or associated with cancer increases directly with the completeness of the data. Such an association is quite impressive in the recent literature. The controversy hinges (1) on whether the "Paget cell" is malignant and (2) on its origin. One view maintains that the epidermal lesion is not cancerous, although it is secondary to an underlying carcinoma; the other that it is cancer, either primary or secondary. Variants of both hypotheses abound.

It is not feasible nor worth while to review critically the abundant and muddled literature of these views, but a brief chronological résumé of the most important as developed by their chief exponents is necessary for adequate orientation. The studies have been made principally on the disease in the nipple.

Paget's (1) description (1874) was strictly clinical. Butlin (54) first studied (1876) the disease histologically. He noted the continuity of the cancer in the milk ducts with the lesion in the epidermis, and considered the latter as primary. Thin (55) in a careful histological study (1881) of four cases of duct carcinoma and Paget's disease was the first to suggest a reverse relationship. In 1889 the French dermatologist, Darier (56), and in 1890 Wickham (57), announced that the disease was an infection caused by "psorosperms," *i.e.* "Paget cells." The influence of this theory was dramatic but short-lived and not long thereafter Darier retracted his statement. In 1894 Unna (58) and others suggested that the characteristic cells were epidermal cells which had undergone a peculiar swelling, and in 1907 von Winiewarter (59) claimed to have traced all the stages from the prickle to the full-blown
<table>
<thead>
<tr>
<th>No.</th>
<th>Date</th>
<th>Author</th>
<th>Age and Sex</th>
<th>Site</th>
<th>Duration</th>
<th>Paget’s Disease</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1874</td>
<td>Paget</td>
<td>?M.</td>
<td>Glans penis</td>
<td>?</td>
<td>?</td>
<td>Clinical mention only</td>
</tr>
<tr>
<td>2</td>
<td>1880</td>
<td>Morris</td>
<td>60F.</td>
<td>Neck</td>
<td>9 yr.</td>
<td>Probably not</td>
<td>Clinical comparison only</td>
</tr>
<tr>
<td>3</td>
<td>1889</td>
<td>Crocker</td>
<td>60M.</td>
<td>Scrotum penis</td>
<td>3 yr.</td>
<td>Yes</td>
<td>Definite alveolar cancer</td>
</tr>
<tr>
<td>4</td>
<td>1891</td>
<td>Tarnovsky</td>
<td>?M.</td>
<td>Penis</td>
<td>?</td>
<td>?</td>
<td>Clinical mention only</td>
</tr>
<tr>
<td>5</td>
<td>1893</td>
<td>Darier and Couillaud</td>
<td>72M.</td>
<td>Scrotum and perineum</td>
<td>15 yr.</td>
<td>Yes</td>
<td>No cancer found</td>
</tr>
<tr>
<td>6</td>
<td>1893</td>
<td>Tommasoli</td>
<td>66M.</td>
<td>Penis</td>
<td>5 yr.</td>
<td>?</td>
<td>“Incipient epithelioma”</td>
</tr>
<tr>
<td>7</td>
<td>1893</td>
<td>Pick</td>
<td>?M.</td>
<td>Glans penis</td>
<td>1½ yr.</td>
<td>?</td>
<td>“Typical cancerous growth”</td>
</tr>
<tr>
<td>8</td>
<td>1894</td>
<td>Ravogli</td>
<td>“Aged” F.</td>
<td>Nose</td>
<td>?</td>
<td>Probably not</td>
<td>Death in several years from metastatic carcinoma</td>
</tr>
<tr>
<td>9</td>
<td>1896</td>
<td>Winfield</td>
<td>??</td>
<td>Lower lip</td>
<td>4 yr.</td>
<td>Probably not</td>
<td>Clinical resemblance; death in year from cancer spread</td>
</tr>
<tr>
<td>10</td>
<td>1897</td>
<td>Shield—also Rolleston and Hunt Dubreuilh</td>
<td>60M.</td>
<td>Penis and scrotum</td>
<td>8 yr.</td>
<td>Yes</td>
<td>Definite alveolar cancer</td>
</tr>
<tr>
<td>11</td>
<td>1901</td>
<td>Morris</td>
<td>51F.</td>
<td>Vulva</td>
<td>3 yr.</td>
<td>Yes</td>
<td>Definite cancer, probably acinar “Alveolar carcinoma”</td>
</tr>
<tr>
<td>12</td>
<td>1903</td>
<td>Holzknecht</td>
<td>?F.</td>
<td>Axilla</td>
<td>12 yr.</td>
<td>?</td>
<td>“Typical cancerous growth”</td>
</tr>
<tr>
<td>13</td>
<td>1903</td>
<td>Matzenauer</td>
<td>44M.</td>
<td>Nose</td>
<td>5 yr.</td>
<td>Probably not</td>
<td>Squamous-cell carcinoma few years earlier “Non-keratinizing” cancer</td>
</tr>
<tr>
<td>14</td>
<td>1904</td>
<td>Jungmann and Pollitzer</td>
<td>46F.</td>
<td>Axilla</td>
<td>13 yr.</td>
<td>?</td>
<td>“Alveolar carcinoma”</td>
</tr>
<tr>
<td>15</td>
<td>1904</td>
<td>Fox and Macleod</td>
<td>65M.</td>
<td>Umbilicus</td>
<td>11 yr.</td>
<td>Probably not</td>
<td>Probably Bowen’s disease</td>
</tr>
<tr>
<td>16</td>
<td>1904</td>
<td>Zieler</td>
<td>42F.</td>
<td>Axilla</td>
<td>5 yr.</td>
<td>Yes</td>
<td>Tubulo-acinar carcinoma in regional lymph nodes</td>
</tr>
<tr>
<td>17</td>
<td>1905</td>
<td>Sequeira</td>
<td>77M.</td>
<td>Penis</td>
<td>2 yr.</td>
<td>?</td>
<td>Carcinoma</td>
</tr>
<tr>
<td>18</td>
<td>1905</td>
<td>Fordyce</td>
<td>60F.</td>
<td>Buttock</td>
<td>6 yr.</td>
<td>Probably not</td>
<td>Followed trauma; basal-cell tumor</td>
</tr>
<tr>
<td>19</td>
<td>1909</td>
<td>Rosenberg</td>
<td>70F.</td>
<td>Vulva</td>
<td>4 yr.</td>
<td>Yes</td>
<td>Carcinoma</td>
</tr>
<tr>
<td>20</td>
<td>1910</td>
<td>Davis (Hartzell)</td>
<td>?M.</td>
<td>Glans penis</td>
<td>?</td>
<td>?</td>
<td>Clinical mention only</td>
</tr>
<tr>
<td>21</td>
<td>1910</td>
<td>Davis (Hartzell)</td>
<td>?M.</td>
<td>Scrotum</td>
<td>?</td>
<td>?</td>
<td>Clinical mention only</td>
</tr>
<tr>
<td>22</td>
<td>1910</td>
<td>Dahring (Hartzell)</td>
<td>??</td>
<td>Perineum</td>
<td>?</td>
<td>?</td>
<td>Clinical mention only; carcinoma</td>
</tr>
<tr>
<td>23</td>
<td>1910</td>
<td>Hartzell</td>
<td>64M.</td>
<td>Forearm</td>
<td>15 yr.</td>
<td>Similar to</td>
<td>Nevocarcinoma</td>
</tr>
<tr>
<td>24</td>
<td>1910</td>
<td>Winfield</td>
<td>?F.</td>
<td>Scapula</td>
<td>8 yr.</td>
<td>?</td>
<td>Nevocarcinoma</td>
</tr>
<tr>
<td>25</td>
<td>1911</td>
<td>Milligan</td>
<td>31F.</td>
<td>Umbilicus</td>
<td>4 yr.</td>
<td>Probably not</td>
<td>Clinical only</td>
</tr>
<tr>
<td>26</td>
<td>1912</td>
<td>Towle</td>
<td>74M.</td>
<td>Interscapular region</td>
<td>25 yr.</td>
<td>Probably not</td>
<td>Epithelioma</td>
</tr>
<tr>
<td>27</td>
<td>1914</td>
<td>Poland</td>
<td>61F.</td>
<td>Cheek</td>
<td>2 yr.</td>
<td>Probably not</td>
<td>Epidermic carcinoma</td>
</tr>
</tbody>
</table>
### Reported Cases of Extramammary Paget's Disease—Continued

<table>
<thead>
<tr>
<th>No.</th>
<th>Date</th>
<th>Author</th>
<th>Age and Sex</th>
<th>Site</th>
<th>Duration</th>
<th>Paget's Disease</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>1914</td>
<td>Grinchar</td>
<td>55F.</td>
<td>Vulva</td>
<td>4 yr.</td>
<td>?</td>
<td>Carcinoma; clinical only</td>
</tr>
<tr>
<td>29</td>
<td>1915</td>
<td>Ormsby</td>
<td>57?</td>
<td>Back</td>
<td>13 yr.</td>
<td>Probably not</td>
<td>12 patches; ? Bowen's disease</td>
</tr>
<tr>
<td>30</td>
<td>1915</td>
<td>Potter</td>
<td>47F.</td>
<td>?</td>
<td>5 yr.</td>
<td>Probably not</td>
<td>? Basal-cell tumor No data</td>
</tr>
<tr>
<td>31</td>
<td>1917</td>
<td>Pospeloff (Sekiguchi)</td>
<td>?M.</td>
<td>Penis</td>
<td>?</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>1917</td>
<td>Kren (Sekiguchi)</td>
<td>?F.</td>
<td>Vulva</td>
<td>?</td>
<td>?</td>
<td>No data</td>
</tr>
<tr>
<td>33</td>
<td>1917</td>
<td>Belot (Sekiguchi)</td>
<td>?</td>
<td>Back</td>
<td>?</td>
<td>?</td>
<td>No data</td>
</tr>
<tr>
<td>34</td>
<td>1917</td>
<td>Sekiguchi</td>
<td>65M.</td>
<td>Scrotum</td>
<td>9 yr.</td>
<td>Yes</td>
<td>Adenocarcinoma in inguinal lymph nodes</td>
</tr>
<tr>
<td>35</td>
<td>1919</td>
<td>Stelwagon</td>
<td>60F.</td>
<td>Nose</td>
<td>?</td>
<td>Probably not</td>
<td>“Clinically suggestive”</td>
</tr>
<tr>
<td>36</td>
<td>1920</td>
<td>Satani</td>
<td>74M.</td>
<td>Axilla</td>
<td>6 yr.</td>
<td>Yes</td>
<td>Carcinoma, ? alveolar</td>
</tr>
<tr>
<td>37</td>
<td>1923</td>
<td>Trimble</td>
<td>63F.</td>
<td>Abdomen</td>
<td>30 yr.</td>
<td>?</td>
<td>? Basal-cell tumor Paget's of bone</td>
</tr>
<tr>
<td>38</td>
<td>1923</td>
<td>Ito</td>
<td>??</td>
<td>Nose</td>
<td>?</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>1925</td>
<td>Arzt and Kren</td>
<td>70F.</td>
<td>Vulva</td>
<td>Several months</td>
<td>Yes</td>
<td>No clinical carcinoma</td>
</tr>
<tr>
<td>40</td>
<td>1927</td>
<td>Van der Hoop, Bonne and Wassink</td>
<td>43F.</td>
<td>Vulva</td>
<td>4 yr.</td>
<td>Yes</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>41</td>
<td>1928</td>
<td>Susman</td>
<td>60M.</td>
<td>Penis</td>
<td>1 yr.</td>
<td>?</td>
<td>Basal-cell tumor</td>
</tr>
<tr>
<td>42</td>
<td>1928</td>
<td>Tashiro</td>
<td>33F.</td>
<td>Vulva</td>
<td>3 yr.</td>
<td>Yes</td>
<td>Cancer not mentioned</td>
</tr>
<tr>
<td>43</td>
<td>1928</td>
<td>Civatte</td>
<td>67F.</td>
<td>Axilla</td>
<td>10 yr.</td>
<td>Yes</td>
<td>Adenocarcinoma, bone metastases</td>
</tr>
<tr>
<td>44</td>
<td>1929</td>
<td>Miescher</td>
<td>74F.</td>
<td>Vulva</td>
<td>?</td>
<td>?</td>
<td>Carcinoma</td>
</tr>
<tr>
<td>45</td>
<td>1929</td>
<td>Petges, Muratet and Lecoultre</td>
<td>?F.</td>
<td>Vulva</td>
<td>4 yr.</td>
<td>?</td>
<td>Cancer not mentioned; also syphilis and trauma</td>
</tr>
<tr>
<td>46</td>
<td>1929</td>
<td>Yoshida</td>
<td>54M.</td>
<td>Penis</td>
<td>14 yr.</td>
<td>?</td>
<td>Cancer not mentioned</td>
</tr>
<tr>
<td>47</td>
<td>1929</td>
<td>Yoshida</td>
<td>54M.</td>
<td>Penis</td>
<td>4 yr.</td>
<td>?</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>48</td>
<td>1929</td>
<td>Yoshida</td>
<td>34M.</td>
<td>Penis</td>
<td>14 yr.</td>
<td>?</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>49</td>
<td>1929</td>
<td>Drake and Whitfield</td>
<td>68F.</td>
<td>Vulva</td>
<td>8 yr.</td>
<td>Yes</td>
<td>“No massive tumor in depth” Clinical only</td>
</tr>
<tr>
<td>50</td>
<td>1930</td>
<td>Susman</td>
<td>66M.</td>
<td>Glans penis</td>
<td>6 yr.</td>
<td>?</td>
<td>Clinical mention only</td>
</tr>
<tr>
<td>51</td>
<td>1931</td>
<td>DaCosta</td>
<td>?M.</td>
<td>Penis</td>
<td>?</td>
<td>?</td>
<td>Clinical mention only</td>
</tr>
<tr>
<td>52</td>
<td>1931</td>
<td>DaCosta</td>
<td>?M.</td>
<td>Penis</td>
<td>?</td>
<td>?</td>
<td>Clinical mention only</td>
</tr>
<tr>
<td>53</td>
<td>1931</td>
<td>Busman and Woodburne</td>
<td>46M.</td>
<td>Glans penis</td>
<td>3 yr.</td>
<td>Probably not</td>
<td>Carcinoma; ? Bowen's type</td>
</tr>
<tr>
<td>54</td>
<td>1933</td>
<td>Glass</td>
<td>76F.</td>
<td>Vulva</td>
<td>?</td>
<td>?</td>
<td>Cancer not mentioned; leukoplakia Polymorphous carcinoma</td>
</tr>
<tr>
<td>55</td>
<td>1934</td>
<td>Louste and Rabut</td>
<td>60M.</td>
<td>Chest and back</td>
<td>15 yr.</td>
<td>?</td>
<td>No clinical carcinoma</td>
</tr>
<tr>
<td>56</td>
<td>1935</td>
<td>Dorfle and Grimm</td>
<td>82F.</td>
<td>Vulva</td>
<td>2 yr.</td>
<td>Yes</td>
<td>No clinical carcinoma No cancer noted</td>
</tr>
<tr>
<td>57</td>
<td>1935</td>
<td>Noguer-More</td>
<td>60M.</td>
<td>Scrotum</td>
<td>2 yr.</td>
<td>?</td>
<td>No cancer noted</td>
</tr>
<tr>
<td>58</td>
<td>1937</td>
<td>Weiner</td>
<td>84F.</td>
<td>Vulva</td>
<td>8 yr.</td>
<td>Yes</td>
<td>Adenocarcinoma</td>
</tr>
</tbody>
</table>
"Paget cell," a claim made again recently (1931) by Ludford (2). Handley's well-known view was first published in 1904 (60a), elaborated in 1917 (60b) and again in 1919 (60c). In his opinion Paget's disease is the result of a diffuse carcinoma of the deeper ducts or acini of the breast. The lymphatics of the corium and subcutaneous tissue are filled by the tumor with resultant edema and associated characteristic epidermal "changes (which) are nutritional and non-malignant."

In 1900 Darier offered another explanation which he gradually elaborated in many articles under the general heading of "dyskeratosis." These views (61) were destined to have a large following. He defined dyskeratosis as "a faulty development of the epidermis in the course of which a certain number of malpighian cells become isolated and differentiated from their fellows, undergoing an abnormal, premature, and imperfect keratinization. These dyskeratotic cells are present in the layers of the epidermis, as far as in the horny layers, in the form of round bodies (corps ronds), granules (grains), globes or corpuscles, with or without nuclei, easily distinguished from the still normal cells as well as from parakeratotic cells" (translated by Fraser, 62). Included in this group of dyskeratoses were (1) Bowen's disease, (2) Paget's disease, (3) dyskeratosis follicularis (Darier's disease), and (4) molluscum contagiosum.

Jacobaeus (63), in 1904, was the first to maintain that not only were "Paget cells" cancer cells from the very beginning but that they were intra-epidermal metastases from underlying glandular carcinoma (i.e. from the lactiferous ducts). He was able, in two of his three cases, to trace direct continuity between the underlying cancer and the intraepidermal "Paget cells." Ribbert (64) in 1904, Kyrle (65) in 1907, and subsequently many German workers adopted Jacobaeus' point of view. In America and in England, however, it has been far from accepted. The influence of Sekiguchi's (33) long and careful study was negligible. Kilgore (66) in 1921, in a study of Bloodgood's material, and Bloodgood (67) himself in 1924 rejected Sekiguchi's conclusion as untenable. They placed the beginning of the disease in the epidermis of the nipple; in their conception it was not necessarily cancer. Ewing (68) also considered Jacobaeus' conception unlikely.

Cheatle (2) in 1923, and again in 1931, concluded that "the clinical signs of Paget's disease can be caused by changes in the epidermic cells alone" and that "in order to be typical the formation of 'Paget cells' from preexisting epidermic cells is essential. The formation of 'Paget cells' may or may not be accompanied by the intraepidermic invasion of neoplastic cells (i.e. from underlying duct cancer). We cannot be sure that the formation of 'Paget cells' is part of a process of neoplasia or merely a process of degeneration."

In Cheatle's opinion, furthermore, the same agents may be simultaneously inducing the epidermic changes above and the cancer changes below and "the agent may be transmitted by the ducts or an agent which has particular affinity for operating in breast epithelium may be blood-borne."

In 1927 Sir Robert Muir (3a) published the first of a series of studies on the subject, espousing and elaborating Jacobaeus' view. Muir was impressed by the ductal distribution of the mammary cancer associated with Paget's disease. Although Butlin (54) had long ago noted such changes in the lac-
tiferous ducts, Muir's elaborate studies showed that Paget's disease of the nipple was, as far as his data indicated, always associated with changes in the duct epithelium. These changes varied from mild hyperplasia to large proliferating cell masses which were indistinguishable from cancer, even though the duct boundaries remained unbroken. The latter, Muir labeled "intraduct carcinoma": it may arise in multiple foci; it grows in the ducts forming a "sort of injection of them" and when it reaches the upper part of the duct it spreads intraepidermally. He defined a "Paget cell" as "a cancer cell growing within a healthy or at least non-neoplastic epithelium." He concluded (1935) that "in the great majority of cases Paget's disease results from an extension of cancerous proliferation from the ducts of the nipple to the surface of the epidermis... an overflow of cancer cells, as it were, to the epidermis with subsequent spread and multiplication therein..." However, he "said 'in the vast majority of cases' because (he) admitted the possibility of the occasional occurrence of a primary epidermal carcinoma with intraepidermal spread..." Of several recent studies which have confirmed Muir's findings, Simard's (5) and Pautrier's (4) are probably the most important.

The clinical and histological findings in our case coupled with a critical review of many reports seem to us consistent with the conception of Jacobaeus and Muir. On the other hand, our data are in many respects incompatible with many of the major premises in the other explanations. A few of the more important considerations involved in this conclusion follow:

It is difficult to conceive of the "Paget cell" as a degenerative phenomenon. Regardless of any other consideration, Handley's conception for instance is dramatically negated by the histology of the present case. In the main vulvar nodule the lymphatics of the dermis are distended with carcinoma and yet the overlying epidermis shows no "nutritional" changes (Figs. 1 and 2). The cell changes are purely those due to compression, the epidermis is flattened and "Paget cells" are absent or infrequent. Yet at the periphery of the nodule, as the lymphatics become less and less involved, the epidermis becomes more and more "pagetized."

The skin lesion shows many of the characteristics associated with cancerous growth:

1. The sharp margins of the lesion, universally recognized, and reminiscent of the spreading lesion in erysipelas; its tendency to spread centrifugally, more or less, in all directions with not infrequent involvement (in the mammary type) of the axilla and entire chest wall—these characteristics, so unlike the usual eczema, are consistent with an advancing intraepidermal carcinoma.

2. Extensive vascularization of the "pagetized" epidermis by capillary-rich fibrous connective-tissue cores growing in from the underlying dermis is a prominent feature of the lesion, and appears proportional to the degree of involvement. Vascularization of the normal epidermis is infrequent and is usually indicative of active cellular proliferation.

3. The "pagetized" epidermis showed all of the cellular variants found in the various metastases. The large round foamy cell (Figs. 5 and 11)—the classical "Paget cell"—was found in the distant rib metastasis. The lacy network seen in the advanced epidermal lesions was frequently observed.
in the abdominal metastases. Vacuolization of the cells was observed both in the epidermis and more distant metastases.

4) In some of our serial sections intraepidermal masses of "Paget cells" (Fig. 2) were in direct continuity with the underlying carcinoma.

5) In the dermis, the involvement by a dense fibroblastic and capillary proliferation, with many lymphocytes and plasma cells (Fig. 8), has long been viewed as a *sine qua non* of genuine Paget's disease. The degree of this involvement varies almost directly with the degree of epidermal involvement. This reaction has always been unclear, although viewed as the reaction to a slow-growing carcinoma it becomes somewhat understandable. And, indeed, in numerous metastases areas were found showing identical reactions.

If then the "Paget cell" is a cancer cell, is it epidermal in origin? Direct continuity between the epidermis and underlying carcinoma has been frequently commented on by many observers: from where to where is the carcinoma travelling? The facts that the carcinoma is, as far as can be told, "ductal" in the breast, and glandular when extramammary, and that it does not otherwise resemble an epidermoid tumor are strongly favorable to an interpretation of intraepidermal invasion from below. Furthermore, analysis of the behavior of the "Paget cell" reveals it to be totally unlike that of epidermal cells. In the early stages of the skin disease the peculiar cells appear almost always in the basal layer, travelling upward as the epidermis becomes more involved (Fig. 3). They fail to keratinize and are shed as rounded cells (Fig. 6) from the desquamating surface. The individual "Paget cell" appears to lie between the epidermal cells, frequently compressing the latter into a series of parallel lines, each cross-barred with intercellular bridges. No intermediate stage between the two types of cells was found and the claims of some writers to have established such a connection remain to date unconvincing.3 Does it seem plausible also to find isolated tumor cells of epidermal origin completely surrounded by normal epidermal cells? The discontinuity of the "Paget cells" in the advancing skin lesion may be very plausibly explained, however, by an epidermotropic, actively invading tumor. For many of the "Paget cells" frequently have long protoplasmic processes which appear to burrow in between two malpighian cells and, indeed, the majority of the "Paget cells" appear to be more or less wedged in between the epidermal cells. Such anatomic peculiarities have led several observers, notably Pauquier, Muir and Simard, to postulate ameboid activity for these cells. Such intraepidermal ameboid activity is not as far-fetched as it may at first seem, for every pathologist is familiar with the isolated polymorphonuclear leukocytes, visible in the epithelium of almost any random section of the tongue, tonsil, or esophagus.

Since nobody has yet satisfactorily proved that Paget's disease can exist independently of an underlying carcinoma, it appears unreasonable to maintain the separateness of the two processes while admitting their coexistence—positions taken, for instance, by Cheatle (1) and Civatte (42). Thus Cheatle is led into the dialectically unnecessary position that "the agent which is

3 The latest of these studies, was made by Ludford (2, p. 342) with great cytological detail. His drawings are indeed unconvincing and a photomicrograph offered presents two cells A and B which appear to be superimposed upon rather than connected to the epidermal cells.
inducing Paget's disease on the surface is also concerned in inducing primary carcinoma in the epithelial cells of the underlying breast."

The frequently slow clinical course has been responsible for a similar diagnostic split. Thus Ewing (68), while not committing himself to a definite histogenesis, believes that the disease occurs in two forms: (a) one in which the characteristic epidermal changes do not extend deeply into the milk ducts, in which no breast tumor is present, in which the course is slow and the prognosis favorable; (b) a rapidly growing but non-definable breast carcinoma, probably from the ducts, spreading to the skin and over the chest, in which the prognosis is highly unfavorable. Arzt and Kren (38) make a similar distinction. The carcinoma is frequently scirrhous and extremely slow-growing, so that with insufficient follow-up or without necropsy the real nature of the disease may be masked. Again, the present case is clearly illustrative. Although indisputably cancer, and although cellular in many areas, in other regions it excited so extensive a connective-tissue reaction that its true malignant nature was masked. It is interesting to recall that several days before the patient's death, one of the many left inguinal skin papules was removed by biopsy and reported by the surgical pathologist as "fragment of skin with chronic inflammatory reaction," although in subsequent re-examination he conceded that it was probably scirrhous carcinoma.

**Nature of the Carcinoma**

Can the histogenesis of the present carcinoma be determined and, if so, does it have any significance? It appears that both of these questions may be answered in the affirmative with a fair degree of surety. On a purely histological basis the glandular nature of the carcinoma has been amply demonstrated above. Acini were frequent and present wherever looked for, sometimes sparse, sometimes numerous. It is noteworthy that in many areas in the vulvar mass apparently normal sweat glands were found intimately mingled with cancerous and aberrant imitations of sweat glands (Fig. 9). Furthermore, evidences of secretion were present in both the original tumor and its various metastases. The fine granules most frequently present in the vacuoles and acinar spaces and reminiscent of the albuminous deposits of edema fluid suggest a watery type of secretion. It may be said with a surety seldom obtained in such histological material that the present case is carcinoma of the sweat gland.

Such a diagnosis would gainsay, at least in this case, the various proponents of an epidermal origin, and would render untenable the objection of Cheatle and Cutler, *viz.* even though direct continuity between the carcinoma and the epidermal lesion were present, it would be difficult to prove that the carcinoma did not grow down from the epidermis.

The significance of such a diagnosis lies in the fact that—when generalized—it explains plausibly many of the peculiarities of Paget's disease. A carcinoma of the sweat gland with secretory activity would offer reasonable explanation for (a) the loosely arranged "Paget cells" which look as if bathed in fluid, frequently and classically found in the full-blown epidermal lesion and found also in this case in the distant metastases, (b) the vacuolization
of both the "Paget" and other tumor cells, and (c) the constant and prominent watery surface ooze, noted by practically all clinical observers on the subject.

It offers, furthermore, a highly suggestive, if theoretical, pathogenesis for this strange malady. The similarity in the clinical history and histological appearance of Paget's disease, regardless of location, calls for such a unitary theory.

The sweat glands in man, it will be recalled, are of two types: the small simple eccrine type and the larger apocrine type. Although the usual type in the lower mammals, in man the apocrine variety is present only in the mammary, axillary, genital, and circumannual region (Trotter, 69; Keith, 70; Richter, 71). It will be remembered further that "there is no longer any doubt that the mammary acini and ducts have been modified from sweat glands" (Keith, 70).

Reference to the analysis of the extramammary cases, earlier in this article, brings forth two startling facts: (a) that the location is in the axilla or anogenital region and (b) where a definite carcinoma is mentioned, it is glandular in type. In the breast "one is impressed with the fact that the records of the literature almost without exception describe and depict the intramammary growth as ductal in distribution" (Eberts, 72).

Is Paget's disease of the skin metastatic carcinoma of the apocrine sweat glands? Several other curious facts make such a speculation more than interesting. There are well known if not completely clear relationships between the apocrine glands and sex activity. Richter (71) quotes Schiefferdecker, who in a comparative anatomical study concluded that the apocrine glands were phylogenetically older than the eccrine, that their function was to elaborate pigments and odors significant for the sex life. "In women the axillary glands appear earlier and are better developed than in man. They show periodic changes during the menstrual cycle and the secretion may cease during pregnancy and at the menopause" (Trotter, 69). Richter (71), who noted that iron pigment and cholesterol were characteristically found in the epithelium of the apocrine glands, observed that these changes appeared first during puberty. The sex preference in Paget's disease may possibly be explained on this basis and may further raise the question whether the secretion of the apocrine glands contains materials with carcinogenic potentialities.

**General Discussion**

Several topics touched upon in the above accounts merit further discussion. Certain superficial resemblances of Paget's disease to Bowen's disease have led to much confusion. That the two are fundamentally different is now clear, but not as well recognized as it should be. This has been thoroughly discussed recently by Wise (73) and Fraser (62).

The rarity of intraepidermal metastases from cancer has also been a stumbling block to many pathologists and is responsible for much of the resistance still offered to this well established phenomenon, pointed out by Jacobaeus as long ago as 1904. It is this which produces the "exquisitely epithelial" (Crosti, 74) picture of Paget's disease. But this form of cancerous spread is not limited to the situations described above. Borst (75),
also in 1904, described small groups of tumor cells in the deeper layers of the normal epidermis at the margin of a small epithelioma of the lip. Arzt and Kren (38) in 1925 described a carcinoma of the rectum with a perineal skin lesion identical grossly and microscopically with Paget's disease. Shaw Dunn (76) in 1930 described a mucinous carcinoma of the rectum with "exquisitely epithelial" metastases to the anorectal squamous epithelium. More recently a similar case was briefly mentioned by Eberts (72). Simard (5), in two carcinomas of the breast with no clinical cutaneous lesions, noted microscopic invasion of the skin simulating Paget's disease. In the malignant nevi and melanomata such intraepidermal spread of the tumor is well known (Cf. Dawson, 27). Hartzell's case, occurring in the forearm, was discussed above. This similarity has even led several students of the disease, as Kreibich (77), Drake and Whitfield (46), and Civatte (42) to suggest that Paget's disease is a nevocarcinoma.

Such findings raise a serious issue: Is there more than a historical validity to justify the maintenance of Paget's disease as either a clinical or pathological entity? It would be rash at the present time to give a definitive answer. But the striking generalizations which the analysis earlier in this paper has permitted are too suggestive to ignore. Even if the skin lesion is not completely sui generis, the maintenance of this disease, linked with an underlying adenocarcinoma, and occurring at specific sites (breast, axilla, anogenital region), as a specific clinico-pathological entity would seem to be warranted.

If the subject is examined from the reverse standpoint—viz., what are the characteristics of sweat gland carcinoma?—practically no help is forthcoming. Although benign tumors of the sweat glands, if uncommon, are well known (Brooke's epithelioma adenoides cysticum, syringocystoma, etc.), carcinoma is a not well defined entity. Ewing (68, p. 884) mentions carcinoma as occurring occasionally and slowly invading the lymph nodes: he does not define its characteristics. The deplorably loose use of the term "carcinoma" by most writers for the benign and obviously non-metastasizing tumor is again demonstrated in the most recent review (Loos, 78). In the literature of Paget's disease, however, from as far back as Crocker (7) the suggestion has been not infrequently made that the associated carcinoma arises in the sweat glands. This point of view has been especially well developed recently by Crosti (74).

Furthermore, although it is important to remember that the potentialities of the basal-cell layer of the epidermis, which many writers stress, may be evoked as a common histogenetic explanation for nevocarcinoma, basal-cell tumor, sweat gland and sebaceous gland carcinoma, still such an explanation, despite its virtue of unity, does not explain many of the above detailed peculiarities. In the light of this, the most acceptable—but admittedly tentative—working hypothesis is proposed: that Paget's disease of the skin is due to intraepidermal metastases of carcinoma of the apocrine sweat glands.

**Summary**

1. Paget's disease, both mammary and extramammary, was first described in 1874, but its nature is still disputed.
2. An instance of the disease occurring in the vulva is reported with detailed necropsy findings.

3. Of 57 other extramammary cases in the literature, no necropsy report is available and only 15 are reported in sufficient detail to warrant a definite diagnosis. An additional 10 are probably Paget's disease.

4. The present case is strongly corroborative of the view of Jacobaeus, Muir, and others as to the nature of Paget disease. This maintains that the skin lesion is the result of intraepidermal metastases from an underlying cancer. That is, the "Paget cell" is a cancer cell.

5. All of the acceptable extramammary cases are located either in the axilla or anogenital region, sites in which the sweat glands are of the apocrine variety. The mammary glands are also modified sweat glands.

6. It is suggested that Paget's disease of the skin is the intraepidermal metastasis from an underlying carcinoma of the apocrine sweat glands. It is noteworthy that in the reported extramammary cases the carcinoma, whenever characterized, is described as glandular in type.

BIBLIOGRAPHY 4


4 References not included here will be found in J. Rousset's monograph, Dyskératinizations épithéliomateuses, Paris, Masson, 1931.
57. WICKHAM, LOUIS: Arch. de méd. expér. et d'anat. path. 2: 46–61, 1890.
75. BORST: Verhandl. d. deutsch. path. Gesellsch. 7: 118–120, 1904.