

SYRINGOCYSTADENOMA PAPILLIFERUM: LIGHT AND ELECTRON MICROSCOPIC STUDIES

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Abstract. Light microscopic and electron microscopic studies of a lesion displaying a typical histopathological picture of syringocystadenoma papilliferum (S.P.) are reported. Light microscopic serial sections showed that the tumor parenchyma extended to the epithelium just above the intrafollicular sebaceous duct. The tumor thus presumably develops from the epithelial region corresponding to the intrafollicular duct of the apocrine sweat gland. Electron microscopy revealed a non-keratinized intracytoplasmic cavity and intercellular canaliculi apparently formed as a continuation of this cavity. Keratinized cells were absent from the glandular and duct epithelium and even from the superficial epithelial portion of acanthotic areas. Neither myoepithelial cells nor secretory granules were identified in areas showing tubular, glandular, or sinusoidal structures. It was concluded that the tumor differentiates towards both the intrafollicular and intradermal duct of the embryonic apocrine sweat gland apparatus.

Key words: Syringocystadenoma papilliferum; Syringocystadenoma papilliferum; Papilliferous syringoadenoma; Na(e)vus syringadenomatosus papilliferus; Skin appendage tumor; Apocrine duct tumor; Intracytoplasmic cavity

Opinions regarding the essential cellular make-up of S.P. are far from unanimous. Since Schiefferdecker in 1917 differentiated apocrine and eccrine forms in the sweat gland apparatus (23), no definite conclusion has been reached as to whether S.P. is apocrine or eccrine in origin.

Light microscopic studies of S.P. have tended to favour an apocrine (4, 18) rather than an eccrine origin (21). Pinkus reported a case of S.P. associated with the eccrine sweat gland apparatus (22). From histochemical and electron microscopic findings, Hashimoto et al. concluded that the S.P. tumor differentiates towards eccrine structures (11, 12), and their monograph (11) classifies S.P. as a tumor originating from the eccrine sweat gland apparatus.

The present study consisted of an examination of serial sections by light microscopy and ultra-microscope. The origin of the tumor is discussed.

MATERIALS AND METHODS

A 4-year-old Japanese girl was referred for examination of a scalp growth which had been present from the age of two. A patchy lesion in the parieto-occipital area had been present since birth and a reddish miliary tumor had appeared on the edge of this lesion after 2 years. The tumor had slowly risen above the surface, increasing in size, and bled easily when injured. The histological diagnosis of the patchy lesion was consistent with infantile nevus sebaceus, while the protruding tumor was a typical S.P.

The tumor was excised completely and divided into two. The larger portion was used for histological examination of serial sections stained with hematoxylin and eosin, Mallory's stain, periodic acid-Schiff stain (PAS) with and without diastase digestion, and Prussian blue and Turnbull blue reactions.

The smaller portion was used for electron microscopic examination. The tissue was cut into 1 mm³ cubes, fixed in 2% glutaraldehyde in 0.1 M phosphate buffer (pH 7.4) for 3 hours, and soaked in 2% sucrose 0.1 M phosphate buffer (pH 7.4) overnight. The cubes were then post-fixed with 1% osmic acid in the same buffer for 2 hours, dehydrated in graded ethanol, and embedded in Epon 812 by the method of Luft (19). Sections were cut in an LKB ultramicrotome and double-stained with uranyl acetate and Reynold's lead citrate. The stained sections were observed in a JEM-100B electron microscope with an accelerating voltage of 80 kV.

RESULTS

Light microscopy

The tumor was mostly above the normal skin level. Invagination of the surface epithelium with the formation of projecting villous and papillary structures was noted. These structures were deeply invaginated, forming cystic spaces and numerous



Fig. 1. Low magnification light micrograph showing a general view of the specimen. The tumor protrudes from the normal skin level and coincides with a long axis parallel to the "long arrow". Large and small asterisks, acanthotic portions; *gl*, eccrine sweat gland; *F*, hair follicle. Double arrow indicates the tumor parenchyma thought to be composed of the intrafollicular portion of the apocrine sweat gland apparatus. Hematoxylin and eosin. $\times 8$.

lumina (Fig. 1). The surface epithelium was composed of several or even numerous squamous cells (asterisked area in Fig. 1).

Both granular and horny layers were absent from the entire surface epithelium of the tumor. Duct and glandular structures opened at unkeratinized surface epithelium (asterisks in Fig. 2A). The papilliferous walls were lined by a double cell layer comprising a thin outer layer of flat epithelial cells and an inner columnar or cuboidal cell layer (Fig. 2B).

The stroma was infiltrated by a dense mass of plasma cells, together with a few lymphocytes, and histiocytes (Fig. 2A, 2B). Hemosiderin-containing cells were occasionally revealed in the stroma by iron staining, but neither the Prussian blue nor Turnbull blue reaction was positive in the tumor parenchyma.

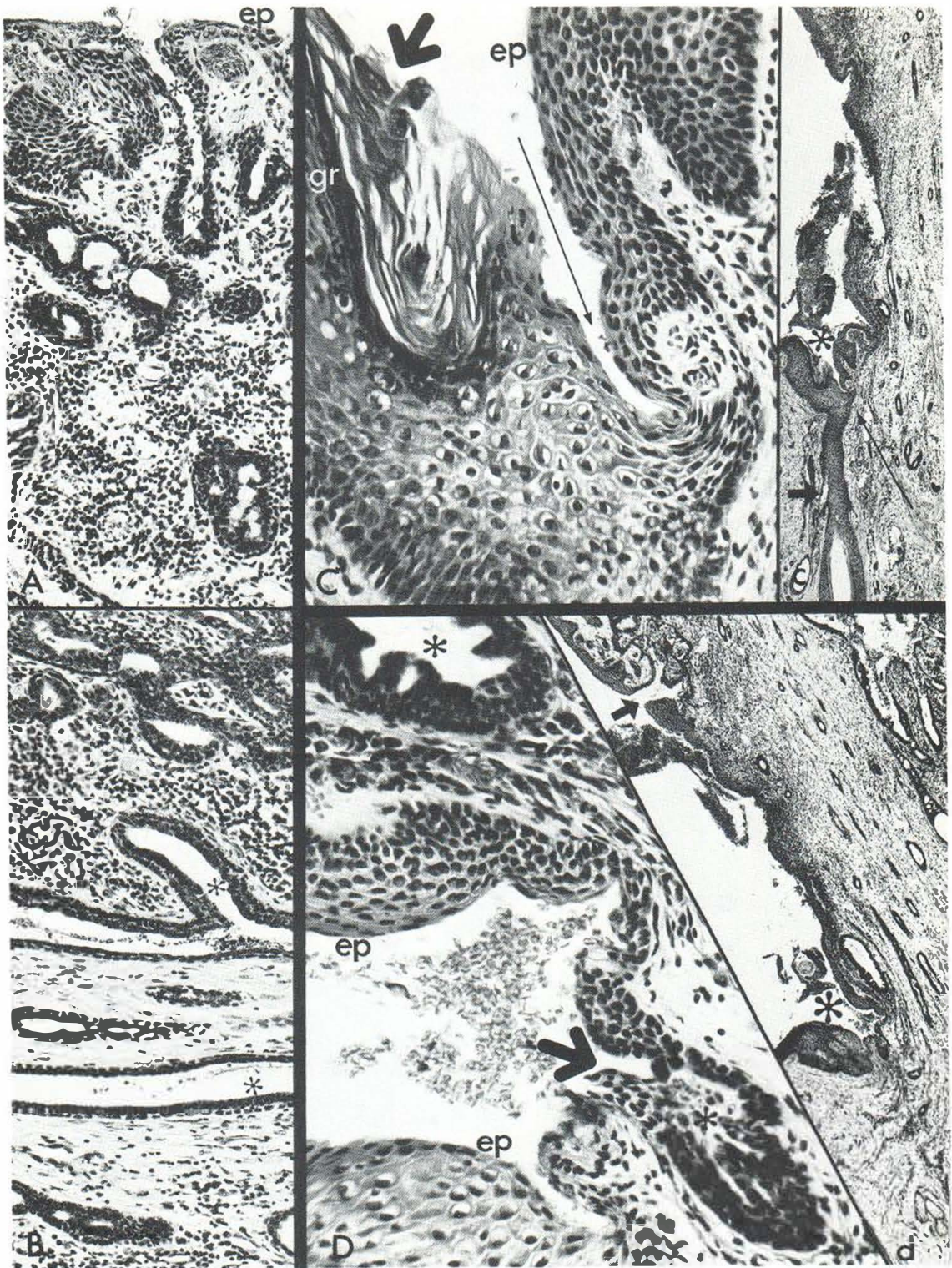
The duct structures (Fig. 2A, 2D, 2d) and glandular structures (Fig. 2D, 2d) never opened onto the surface epithelium unless this was un-keratinized, and the tumor parenchyma (*ep* in Fig. 2C) extended only to the uppermost area of the hair follicle (thin arrows in Fig. 2C, 2c), without continuing to the normal epidermis.

These findings strongly suggest that the tumor parenchyma is restricted to non-keratinized epithelium, presumably the portion corresponding to the intrafollicular epithelium of the apocrine sweat gland apparatus.

Electron microscopy

At low magnification, the parenchyma cells constituting the acanthotic epithelium gradually flattened towards the surface of the tumor (Fig. 3A). Although the arrangement of these squamous cells was very similar to that in normal epidermis, neither keratohyalines nor Odland bodies were detected in the cells. Furthermore, keratin layers were absent from the surface of the epithelial cells ("sur" in Fig. 3A). An intracytoplasmic cavity followed by two intercellular canaliculi were readily distinguishable in progressing from the deep region to the surface region of the epithelium ("1", "2" and "3" in Fig. 3A) suggesting that a structural sequence existed in these formations. The cell forming the intracytoplasmic cavity was connected to the surrounding squamous parenchyma by desmosomes and had a prominent nucleolus (Fig. 3B). The cavity-forming cell contained mitochondria, free ribosomes, rough-surfaced endoplasmic reticulum, tonofilaments, and a few lysosomes.

Fig. 2. (A) Ductal structure (asterisks) open to non-keratinized surface epithelium (*ep*). $\times 70$. (B) At the central portion of the tumor, the ductal structures are largely composed of a round or cuboidal outer cell layer and a cylindrical or columnar inner cell layer (asterisks). $\times 70$. (C) An enlargement of the area between the asterisk and long thin arrow in Fig. 2c. The thin long arrow indicates the very sharp demarcation between non-keratinized tumor parenchyma (*ep*) and keratinized normal epidermis (thick arrow). *gr*: granular layer. $\times 350$. (D) An enlargement of the asterisked area in Fig. 2d. A distinct and close interrelationship is evident in the pattern between the non-keratinized superficial epithelium (*ep*) and glandular structures (asterisks) of the tumor. (c, d) These low magnification pictures are presented for easy understanding of the tumor origin and its relationship with (C) and (D) respectively. $\times 30$. Thick arrow in Fig. 2c: sebaceous gland.



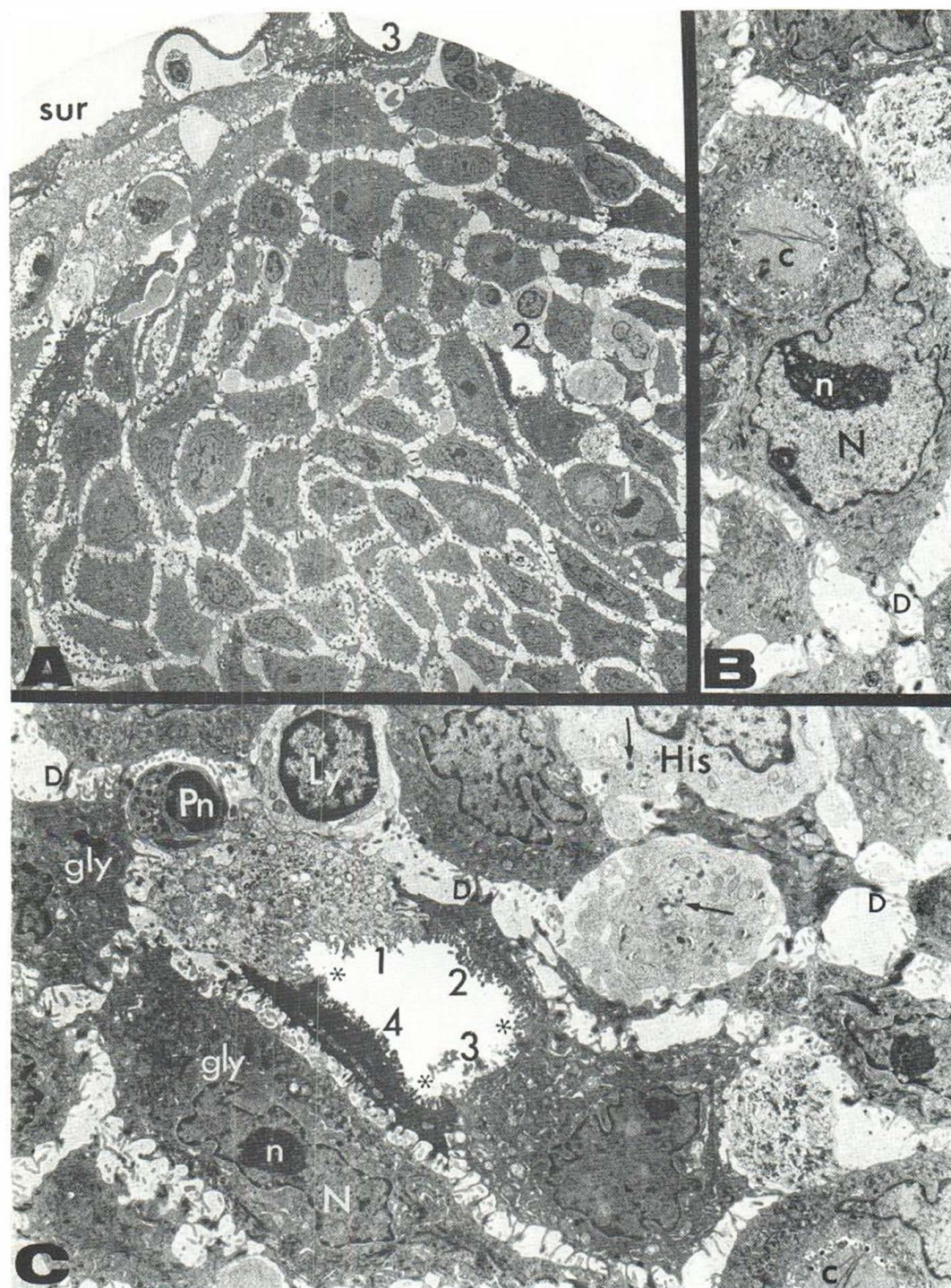


Fig. 3. (A) An acanthotic area. A fairly close consecutive relationship can be seen between the intracytoplasmic cavity forming cell (1) and intercellular canaliculi (2) (3). $\times 1300$. (B) Intracytoplasmic cavity forming cell. *c*, intracytoplasmic cavity; *N*, nucleus; *n*, nucleolus; *D*, desmosome. $\times 4800$. (C) Intercellular canaliculus com-

posed of four cells with different densities (1, 2, 3, 4). Asterisks, villi; *D*, desmosomes. Lymphocyte (*Ly*), polymorphonuclear leukocyte (*Pn*), and lysosome-contained histiocyte (*His*) are visible in the parenchyma cells. $\times 4800$. Arrow, lysosomes; *gly*, glycogen; *N*, nucleus; *n*, nucleolus.

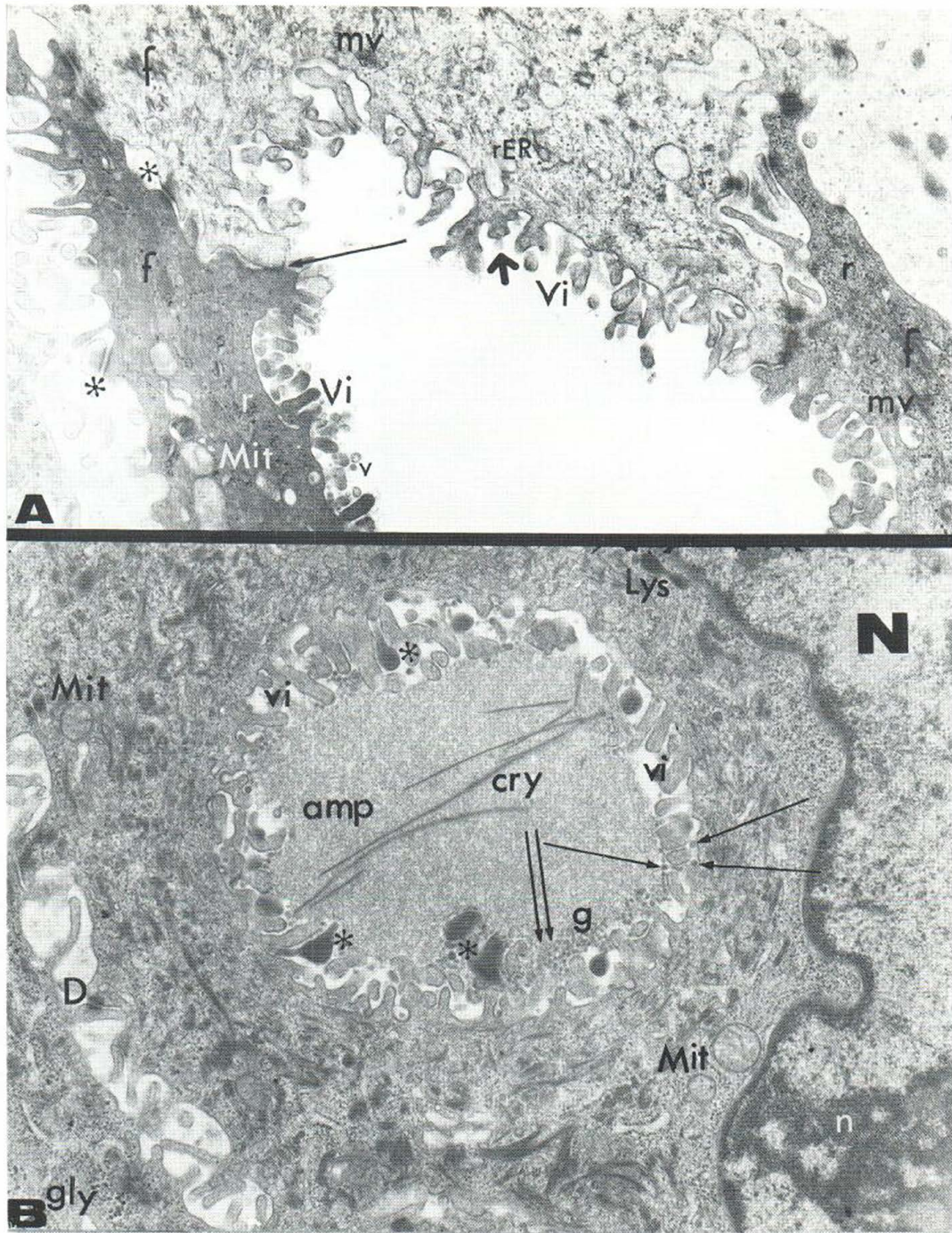


Fig. 4. (A) Enlargement of the upper half of the intercellular canaliculus in Fig. 3C. Many organelles are found in each cell, but keratohyalin, Odland bodies, and keratinization are never found in these areas. $\times 29\,000$. f, tonofilament; Mit, mitochondria; Asterisks, desmosomes; mv, multivesicular body; rER, rough-surfaced endoplasmic reticulum; r, free ribosomes; arrow, tight

junction; Vi, villi; v, pinched-off villi; thick arrow, microapocrine phenomenon. (B) Intracytoplasmic cavity. Vi, microvilli; Asterisks, electron-dense substance; g, granule like structures; amp, amorphous substance; cry, fibrin-like substance; Mit, mitochondria; Lys, lysosome; N, nucleus; D, desmosome; gly, glycogen particles in one of the adjacent parenchyma cells. $\times 15\,000$.

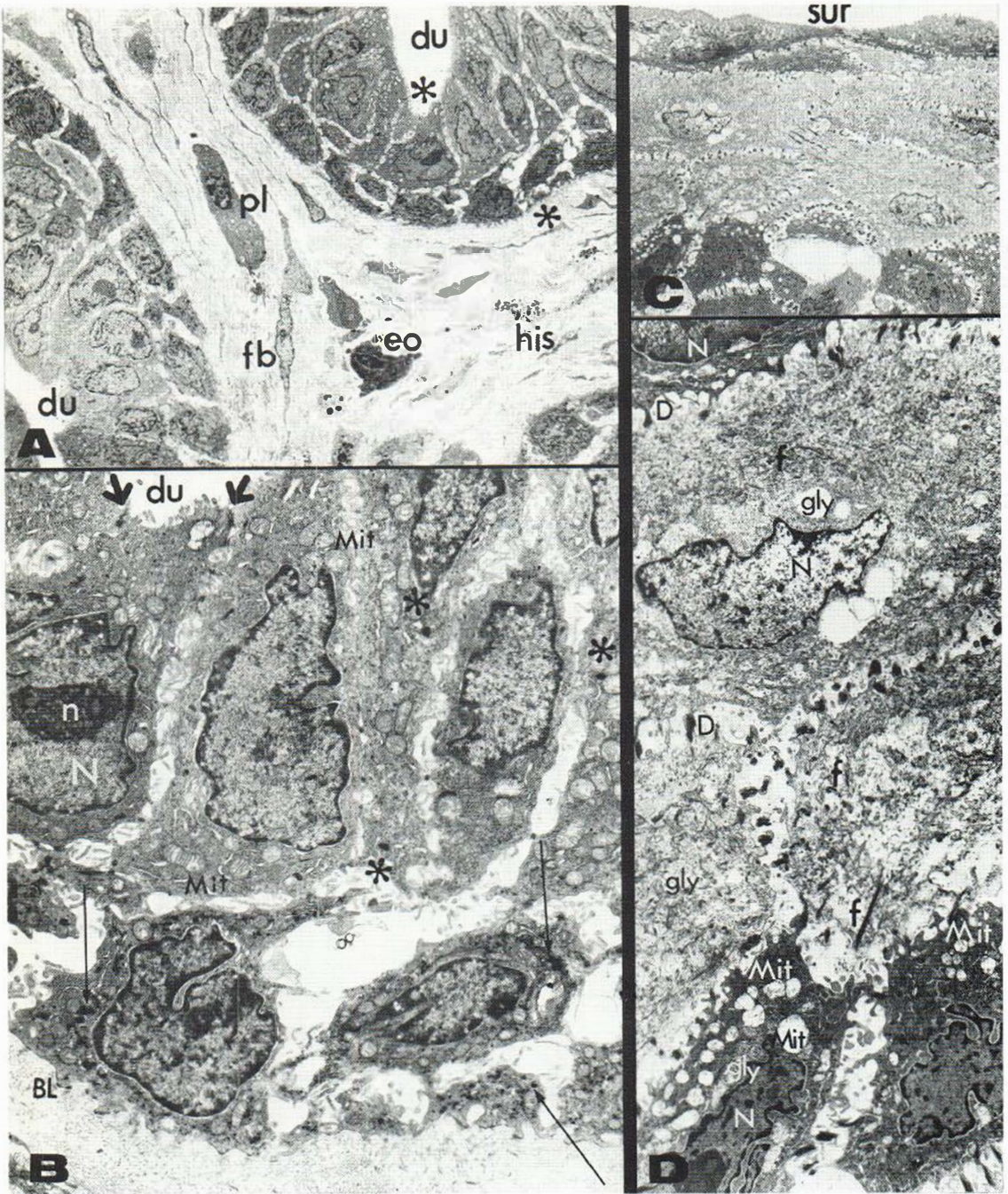


Fig. 5. (A) Two ductal structures and stroma. Each lumen (*du*) is surrounded by two to three cell layers. Fibroblast (*fb*), histiocyte (*his*), plasma cell (*pl*), and eosinophil (*eo*) are found in the stroma. $\times 1400$. (B) Enlargement of ductal epithelium in the area between asterisks in Fig. 5A. A tight junction and terminal bar seal the luminal end of the cell-to-cell contact between neighbouring columnar inner cells (*thick arrows*). There are a few lysosomes (*asterisks*), but none of the specific secretory granules usually found in the secretory cell of the normal sweat gland apparatus can be found. $\times 5700$. (C) Surface epithelium of the tumor. It is composed of several or more squamous cells, but no evidence of actual keratinization is found. That is, keratin layers, keratohyalines, or Odland bodies are undetected in this area. *sur*, external surface of the tumor. $\times 1300$. (D) Enlargement of the asterisk marked area in Fig. 5C. *N*, nucleus; *D*, desmosome; *gly*, glycogen; *f*, tonofilament; *Mit*, mitochondria. $\times 5100$.

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Keratohyalin and Odland bodies could not be found in the cytoplasm (Fig. 4B). The cavity was lined by numerous microvilli and filled with amorphous matter (Fig. 4B), which was found to contain a fibrinoid substance (*cry*), a desmosome-like substance (asterisked), and a granuloid substance (single arrow, double arrow). However, none of these substances displayed the corresponding well-known cellular structures. Thus, the fibrinoid substance did not have the striation of about 20 nm periodicity characteristic of fibrin; and although the electron-dense matter indicated by asterisks in Fig. 4B were first thought to be desmosomes, this possibility was ruled out by the serial sections. Some of the granuloid structures were delimited by a trilaminar membrane (arrows in Fig. 4B) and gradually merged into the amorphous substance (double arrow in Fig. 4B). The contents of the granuloid structures and trilaminar membrane were very similar in quality to those of the microvilli. It was concluded, therefore, that the amorphous substance in the cavity derived not from outside the cell but from the cellular cytoplasmic components themselves.

The lumen of the intercellular canaliculus located just above the intracytoplasmic cavity consisted of a single layer of four cells in slightly differing stages of maturation (Fig. 3C).

The luminal margin of each cell possessed numerous microvilli. The cells were inter-connected by desmosomes and a junctional complex, and were connected to the surrounding squamous parenchyma cells by desmosomes (Fig. 4A). The lumen contained pinched-off villi and at the top of one of the luminal villi there was a break in the plasma membrane, with a discharge of small amounts of cell content into the lumen (thick arrow in Fig. 4A).

The cells constituting the intercellular canaliculus contained sparse free ribosomes, mitochondria, rough-surfaced endoplasmic reticulum (rER), tonofilaments, and multivesicular bodies. However, no peripheral band of tonofilaments, keratohyalines, and keratinization, was found in these cells (Fig. 4A). Some cells appeared clear, while others were dark. The difference in density was attributed to a variation in the electron-density of the cell matrices (Fig. 4A) rather than a difference in kind or quantity of cell organelles such as free ribosomes, rER, glycogen particles, and tonofilaments.

The duct epithelium of the lumen was surrounded

by two or three concentric cell layers, i.e. a layer of inner cells, sometimes a layer of medial cells, and an outer layer of basal cells. The luminal cell of the duct epithelium possessed a little apical cytoplasm and luminal microvilli (Fig. 5A), and contained prominent mitochondria, diffuse sparse free ribosomes, rER, a small quantity of tonofilaments, glycogen particles, and rarely, a few small lysosomes. No secretory granules could be detected, however (Fig. 5B). No periluminal band of tonofilaments and keratinization was found, either. The contact between neighbouring luminal cells at the luminal end was usually achieved by a tight junction and terminal bar (Fig. 5B). The cells of the medial layer had the same characteristics as the inner cells except that the luminal border was absent. The cells of the basal layer contained numerous aggregated glycogen particles, in contrast to the negligible amount in the other two layers; on the other hand, there were fewer tonofilaments. The dark appearance of the basal cells was ascribed to the same effect as noted in the luminal cell of the intercellular canaliculus in Fig. 4A. The outer plasma membrane of the cells rested on a continuous basal lamina (Fig. 5B).

Although the duct cell nucleus very occasionally contained one large nucleolus (*n* in Figs. 2B, 5B), atypical cells suggestive of malignancy were not observed within the scope of the present examination.

No evidence of actual keratinization (Fig. 1) could be found. In other words, no keratin layers, keratohyalin, or Odland bodies could be undetected in the present study (Figs. 5C, 5D).

A few polymorphonuclear leukocytes, lymphocytes and histiocytes had infiltrated among the tumor parenchyma cells, some of the histiocytes containing mitochondria, rER, free ribosomes, and several lysosomes (*His* in Fig. 3C). Melanocytes and Langerhans cells were not observed.

COMMENT

Syringocystadenoma papilliferum (S.P.) was first reported as a tumor of sweat gland origin by Peterson in 1892 (20). Since Shiefferdecker's differentiation of the sweat glands into apocrine and eccrine in 1917 (23), attempts to prove the apocrine or eccrine origin of the lesion have led to considerable controversy. Lever (18) insisted on the primary epithelial germ theory. Pinkus has reviewed the

Table I. *The present findings of the intrafollicular and intradermal duct portions of an apocrine sweat gland apparatus*

	Keratinization (+kerato- hyaline granules)	Luminal villi	Multivesicular dense bodies	Periluminal filamentous zone	Myoepithelial cell	Secretory granules
Apocrine						
Intra follicular duct	—	+	+	+	—	—
Intra dermal duct	—	+	—	+	—	—
Secretory segment	—	+	—	—	++++	—
Eccrine						
Intra epidermal duct	+	++++	++++	+++	—	—
Intra dermal duct	—	++	—	+	—	—
Secretory segment	—	+	—	—	++++	—
Case	—	+	±	±	—	—

dynamics of S.P. (22) and concluded that the histogenesis of S.P. is multiform, i.e. whereas most cases originate from proliferated mature apocrine sweat gland apparatus, some are associated with the eccrine sweat gland or originate from pluripotential cells in the adult epidermis stimulated by trauma or by unknown factors.

From histochemical and electron microscopic findings, Hashimoto and co-workers (11, 12) reported that S.P. is a tumor differentiating towards eccrine structures, and therefore classify S.P. in their monograph (11) as a tumor of eccrine sweat gland origin.

Although the application of light microscopic methods to distinguish apocrine and eccrine sweat gland apparatus has occasionally been described (2, 3, 14), none of these histological techniques supplies enough evidence to confirm the difference between the two kinds of apparatus, especially in pathological conditions such as tumors and nevi. Demonstration of apocrine secretion in normal eccrine sweat gland secretory cells at the light microscopic level as well as by electron microscopy would constitute an ideal proof to resolve the controversy (16, 17).

One of the most salient findings of the present

light microscopic study of serial sections is that the tumor develops from unkeratinized epithelium, extending to the epithelium just above the intrafollicular area of the sebaceous gland, which corresponds to the intrafollicular part of the apocrine sweat gland apparatus. Vohwinkel (24) noted that the surface of the S.P. tumor is open to the normal epidermis and for this reason alone he was sceptical of an apocrine origin, though he also admitted that the histological pattern and cell components in the case studied revealed apocrine structures. Schiefferdecker (23) did not discount the possibility of some normal apocrine ducts open to the epidermis, but Hashimoto (10, 13) has challenged

Table II. *Summary of the present findings*

	Intracytoplasmic cavity		
	Apocrine	Eccrine	Case
Luminal villi	+	++++	+
Multivesicular dense bodies	+	++++	+
Keratohyaline granules	—	+	—
Keratinization	—	+	—

this view by pointing out that a secondary epithelial germ very close to the primary epithelial germ could easily be mistaken for an apocrine gland anlage. Another point which must be emphasized in this context is that the intrafollicular apocrine duct originates high in the follicular wall or sometimes in the epidermis next to the follicle (21).

Hashimoto has discussed the ultramicroscopic morphology of both types of sweat gland in detail as regards the normal embryonic and adult sweat gland apparatus (5, 6, 7, 8, 9, 10). These studies show conclusively that there are well defined differences between (i) the intrafollicular apocrine duct, (ii) the intra-epidermal eccrine duct, and (iii) the secretory segment of both kinds of gland. In comparison with some of the distinctive electron microscopic findings in Hashimoto's papers, the present studies are summarized in Tables I and II. The inevitable conclusion is that S.P. is an embryonic, less mature (organoid), tumor originating from the intrafollicular and dermal duct portion of the apocrine sweat gland. The possible origins would then be: (i) a dysembryogenetic involvement of the anlage—the primary epithelial germ—together with nevus sebaceus; (ii) formation from the "heterotopic" apocrine gland found almost invariably in the adult head and face (13); or (iii) a hamartoma originating in the regressed apocrine sweat gland found over almost the entire body as a normal part of early embryonic hair anlage (15).

Pinkus (21) suggested that some cases of S.P. could originate from pluripotential adult epithelial cells of the skin. However, this hypothesis would appear to be based on the classic theory of cell differentiation of Weismann (25), i.e. the proliferating cell is regarded only as a kind of multi-potential germinative cell.

A recently proposed theory of human cell differentiation postulates that tissues or organs are irreversibly restricted by major differentiation (1), this effect being undiminished by replication of cell mitotic cycles. Moreover, cell differentiation ensues only within the minor differentiation (1), which is limited by the above-mentioned major differentiation.

It is accordingly difficult to agree with Pinkus's particular views on the histogenesis of some S.P., especially since (i) with the exception of metaplasia, few, if any, reversible transitional forms between different tissues or organs are known, (ii) oncologists generally accept that the tumor does not

show a sufficiently immature status of differentiation to be considered absolutely de-differentiated but has instead a status within the range of dys-differentiation of the original tissue or organ.

Obviously, in consequence of Hashimoto's electron microscopic findings (12), cases of eccrine origin or structure cannot be ruled out. Nevertheless, the present findings raise serious doubts as to the classification of S.P. as a tumor solely of eccrine origin.

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