Evolution of a Dermatopathologist A 35-year Experience

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This year marks the 35th years of my career as a dermatopathologist. Following completion of three years of dermatology residency in Philadelphia and in Wisconsin in 1959, I was granted a two-year dermatopathology fellowship with Professor Hermann Pinkus at Wayne State University, at that time a very rare opportunity. Dr. Pinkus and I formed an association that lasted more than 25 years. Dr. Yutaka Mishima, a young Japanese dermatologist had just arrived a few months before and was setting up a laboratory for pigment cell research and electron microscopy. I was more interested in techniques of tissue preparation and special histochemical stains specifically in the areas of acid mucopolysaccharides and the elastic fibres.

In 1959, we had in our disposal PAS, Verhoff, aldehyde fuchsin, acid orcein, toluidine blue, alcian blue, and colloidal iron stains that we could use with or without enzymes such as amylase, elastase or hyaluronidase for proper substance identification. Pinkus, utilizing alcian blue-PAS combination some two years before had identified alopecia mucinosa characterized clinically by inflammatory plaque and alopecia.[1] We expanded this entity by recognition of cases that were not inflammatory, lesions outside of the head and neck areas and a subset that occurred in older individuals with disseminated plaques as a manifestation of mycosis fungoides.[2] Next came an interesting series of cases with extensive papular lesions, eventually coalescing to form sclerodermoid thickening of the skin as examples of scleromyxedema.[3] Histologically, these were found to be different from papular mucinosis by having extensive dermal histiocytic proliferation in predominantly perifollicular arrangement, in addition to positive staining with alcian blue at PH. 3.2 and with aldehyde fuchsin suggesting the presence of both hyaluronic acid and sulfated acid mucopolysaccharide. These cases further proved to have a systemic disease having associated endocrine abnormalities and abnormal serum globulins.

Aldehyde fuchsin is a beautiful stain for elastic fibres and for sulfated acid mucopolysaccharide and is useful for identification of extramammary Paget's disease. It is, however, not practical for routine application because other skin tissue components are not identified. Pinkus created acid orcein-Giemsa combination as a complete stain that shows all tissue elements in addition to the elastic fibres.[4] Our initial investigations into the elastic fibres included new formation of the elastic fibres in pigmented nevi,[5] in some basal cell epitheliomas,[6,7] in various

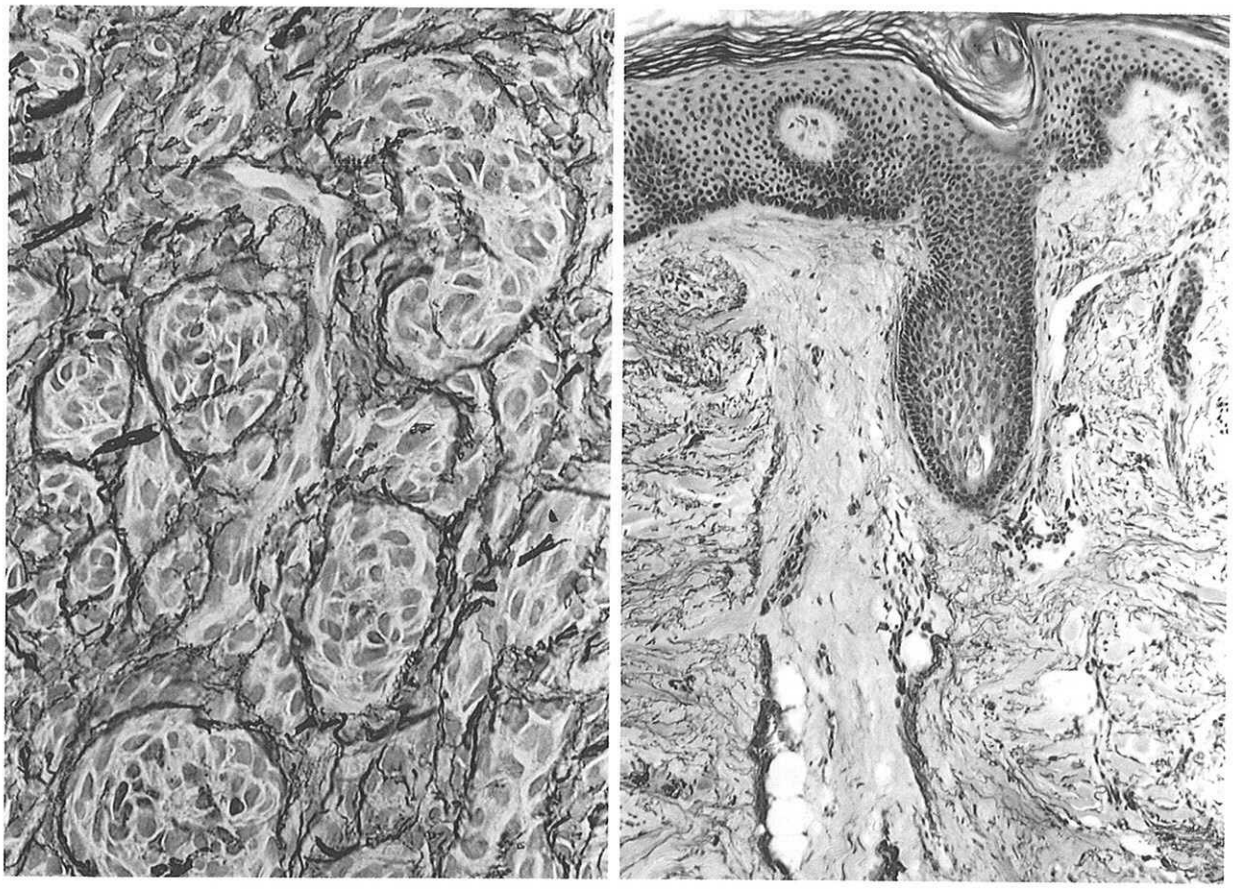

Fig. 1: Left. Congenital melamocytic nevus shows a network of elastic fibres surrounding nests of nevus cells. Acid orcein-giemsa, x 180. Right. Scaring alopecia shows remnant of elastic tissue left behind from an atrophic hair follicle. Acid orcein-giemsa. X-125.

dermal elastoses and in the histopathology of striae distensae. [8,9]

A practical finding was new formation of elastic fibres in congenital melanocytic nevi and their absence in malignant melanomas. Elastic stains also proved useful in differentiation of scarring from non-scarring form's alopecia (Fig. 1). We investigated a series of infants and children with cutis laxa (systemic elastolysis) clinically characterized by excessive soft and wrinkled skin and systematically by the presence of bullous emphysema, hernia and vascular complications.[10] Excessive breakdown of elastic fibres was demonstrated in the loose skin, in the alveoli of the lungs and in the wall of large blood vessels.

The next study concerned with a series of 13 cases with elastosis perforans serpiginosa.[11] A significant clinical finding was the association with Downs syndrome, Ehlers-Danlos, pseudoxanthoma elasticum, Marfan's syndrome and osteogenesis imperfecta in approximately 25% of the cases. Classic skin lesions are circular or circinate, located over the sides or back of the neck, but may be located elsewhere. Histologically, focal increase in dermal elastic fibres occurs in association with multiple perforating channels through which some eosinophillic elastic fibres mixed with degenerated cell debris are eliminated. During the histologic investigation

of elastosis perforans serpiginosa, it became obvious that the epidermis and the follicular epithelium have the potentiality to react in a specific manner aimed at elimination of unwanted material form the dermis to the outside. Transepidermal elimination of inflammatory cells, histiocytes, abnormal lymphoid tissue and some infectious organisms was a routine observation. Elimination of other tissue components such as elastic fibres, collagen bundles, calcium or bone required a more complicated tissue reaction including pseudoepitheliomatous hyerplasia and formation of perforating channels. The list of "perforating dermatoses" included elastosis perforans serpiginosa, reactive perforating collagenosis, perforating folliculitis, perforating eruption in patients with chronic diabetes, perforating granuloma annulare, perforating pseudoxanthoma elasticum and chondrodermatitis nodularis of the ear.[12] An illustrative example is calcium chloride necrosis which occurs when calcium chloride comes in contact with the wet skin or following electroencephalography in places where the electrodes are applied to the scalp.[13,14] Massive calcium salt is deposited in the upper dermis to which the epidermis reacts with pseudoepitheliomatous hyperplasia and formation of perforating channels through which calcium particles are eliminated.

At the same time, we also identified a new disease, a counterpart to the elastosis perforans serpiginosa in which abnormal reactivity of collagen is involved under the term "reactive perforating collagenosis".[15] This appears predominantly in early childhood and can be familial. In response to minor trauma, small skin colour papules appear that soon become centrally umbilicated containing a core of adherent material. The lesions last six to eight weeks and eventually disappear without scar formation. Linear lesions occur suggesting Koebner phenomenon and lesions can be induced by superficial scratches. Sibling and families with several members affected have been reported from India and Saudi Arabia. The initial histologic changes include strong basophilia of the papillary collagenous tissue and a few scattered inflammatory cells. Umbilicated lesions show vertical bundles of collagenous tissue entering into the overlying epidermis.[16] Collagen bundles mixed with keratin and inflammatory cells form the central plug of the umbilicated lesion. Once the supply of abnormal collagen is exhausted, the epidermis repairs itself and the area heals without scar formation. In the following years, a number of cases with scattered and somewhat larger lesions, but histologically similar to the reactive perforating collagenosis, were reported in adults with chronic diabetes undergoing renal dialysis.

Pinkus was the first to stress that the skin can react to various injurious agents through only limited forms of tissue changes, the most common of these being eczematous, psoriasiform and lichenoid tissue reactions. This was our approach to the histologic differential diagnosis of the inflammatory dermatoses presented in the first edition of our book in 1969 and has continued up through the coming sixth edition.[17]

The eczematous tissue reaction classically seen in an acute eczematous contact dermatitis is histologically characterized by the presence

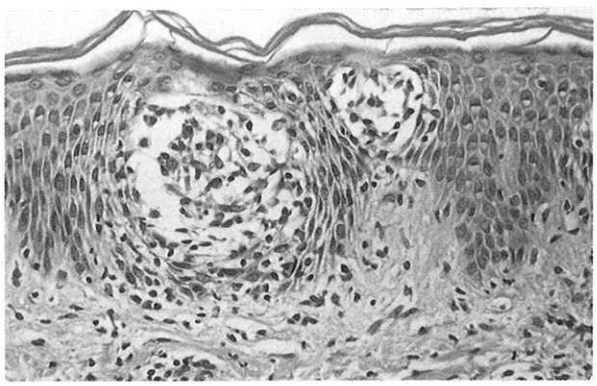

Fig. 2: Eczematous tissue reaction is characterized by spotty areas of spongiotic edema and exocytosis resulting in formation of intraepidermal vesicles. H&E. X-125.

in spotty fashion areas of intracellular and intercellular edema and exocytosis of inflammatory cells leading to spongiosis and intraepidermal vesicle formation (Fig. 2). Subsequently, there is loss of the granular layer, parakeratosis and crusting. Dermal perivascular inflammatory cell infiltrate is superficial and consists predominantly of lymphocytes. Table (1) lists diseases that show an eczematous type of tissue reaction.

TABLE 1. ECZEMATOUS (SPONGIOTIC) TISSUE REACTION

Allergic Eczematous contact dermatitis
Primary irritant dermatitis
Dyshidrosiform dermatitis
Nummular eczema (dermatitis)
Photocontact and phototoxic dermatitis
Asteatotic dermatitis
Superficial dermatophytosis
Pityriasis rosea
Infantile acropustulosis
Erythema toxicum neonatorum
Acrokeratosis paraneoplastica

Psoriasiform tissue reaction was investigated in two publications. The initial histologic features involve papillary blood vessels squirting serum and exudate into the suprapapillary epidermis. [18,19,20] Disruption of basement membrane is observed at the initiation of this process followed by spongiotic edema and exocytosis of inflammatory cells leading to spotty loss of the granular layer and mound-like parakeratosis (Fig. 3).

In seborrheic dermatitis, squirting of serum and exudation occurs in distant papillae resulting in formation of a few and widely spaced mound-like areas of parakeratosis. In psoriasis, however, this process occurs more regularly and in every papillae resulting in extensive loss of keratinocytes within the suprapapillary epidermis. In response to the rapid loss of the suprapapillary plate, the epidermal rete ridges become long and club shaped and show significant increase in the number of mitotic figures, not only in the basal but in several rows of cells above the basement membrane.

The hallmark of a lichenoid tissue reaction is a primary insult to the basal cells of the epidermis initiating a cascade of epidermal and dermal reactions.[21] Degeneration of basal cells is initially associated with loss of pigment into macrophages and a band-like lymphocytic

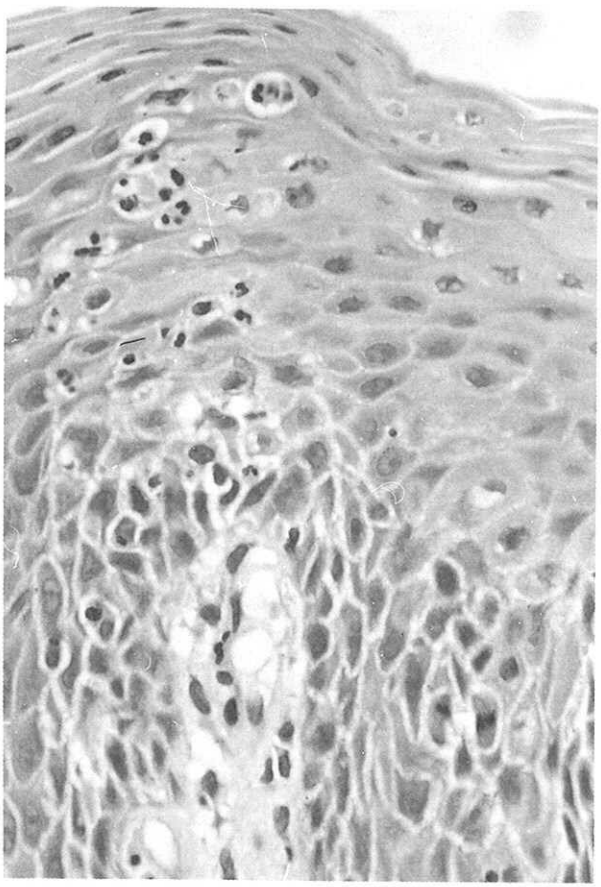

Fig. 3: Psoriasiform tissue reaction is characterized by suprapapillary areas of spongiotic edema and exocytosis with loss of granular layer and parakeratosis. H&E. X-225

inflammation (Fig. 4). The epidermal reaction includes hypertrophy of prickle cells, retention of granular cells and compact orthokeratotic hyperkeratosis. It appears now that a T-cell

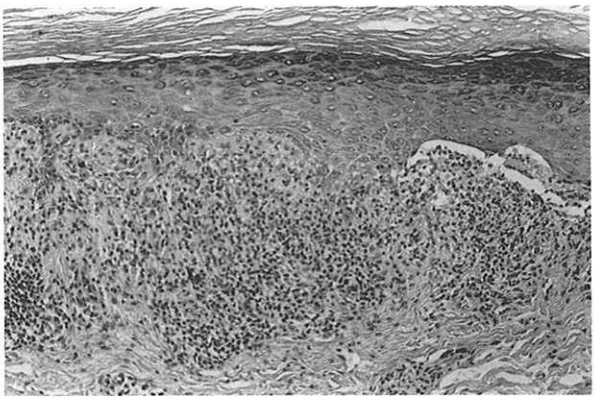

Fig. 4: Lichenoid tissue reaction is characterized by extensive liquefaction degeneration of basal cells and a close band-like lymphocytic infiltrate. Note also marked hypergranulosis and orthokeratotic hyperkeratosis. H&E. X-125.

mediated immune attack to the epidermis is responsible for development of a lichenoid tissue reaction. A list of skin lesions exhibiting a lichenoid type of tissue reaction is given in Table (2).

The next subject is porokeratosis of Mibelli in which a clone of abnormal keratinocytes expand peripherally into a circle and in which the characteristic cornoid lamella, depending on the time and location, may be found within the epidermis, in sweat ducts or within the infundibulum of hair follicles. The cornoid lamella may be single, double or multiple, it may be small as in the superficial actinic lesions or insignificant in facial lesions. Clinical forms include the classic Mibelli type, disseminated superficial actinic form, multiple punctuate palmo-plantar, nevoid linear, facial, mucosal and the solitary discrete planter varieties.[22,23,24,25] Facial porokeratosis appears to be predominantly a disease of the Middle East.

Hermann Pinkus and I had equal interests in adnexal tumours of the skin and made a number of contributions. Premalignant fibroepithelial tumour and eccrine poroma were identified before I had arrived. In 1961, we presented a scientific exhibit on adnexal tumours of the skin at the annual meeting of The American Academy of Dermatology and the AMA. Contributions made in this field in the following years included some eight originally described entities. In a critical review in 1964, we pointed out that the majority of the lesions diagnosed as Jadassohn's intraepidermal epithelioma are the clonal variety of a seborrheic verruca.[26] In these lesions, the intraepidermal islands of

TABLE 2. LICHENOID TISSUE REACTION

Dermatoses with lichen planus-like pattern

Lichen planus
Lupus erythematosus
Lichen nitidus
Lichen planus-like keratosis
Lichenoid drug eruption
Lichen planus actinicus
Keratosis lichenoides chronica
Lichenoid photodermatitis
Lichen pigmentosus
Lichen sclerosus et atrophicus

Dermatoses with poikilodermatous pattern

Poikiloderma congenitale
Poikiloderma atrophicans vasculare (Jacobi)
Poikiloderma related to dermatomyositis
Poikiloderma related to lupus erythematosus
Poikilodermatous parapsoriasis en plaques
Poikiloderma of Civatte
Hereditary sclerosing poikiloderma
Hereditary acrokeratotic poikiloderma

Pigmented dermatoses

Invontinentia pigmenti
Lichen striatus
Erythema dyschromicum perstans
Riehl's melanosis
Graft vs host disease
Regressing melanoma

small basaloid cells are not very sharply defined and merge with the surrounding keratinocytes. Some islands are deeply pigmented and include a population of dendritic melanocytes. Another form of intraepidermal epithelioma is hidroacanthoma simplex, characterized by well-defined islands of small cuboidal cells similar to those of eccrine poroma, but in confine to the epidermis.[27] The tumour cells contain glycogen and today we know that they also stain with eccrine specific antibodies.

Tumour of follicular infundibulum was described in 1961 and again in 1971. The initial case was a middle aged woman with multiple light colour facial lesions.[28,29] Histologically, (Fig. 5) this showed proliferation of outer root sheath epithelium forming a fenestrated plate beneath the epidermis. Small hair follicles appear to enter and disappear within the lesions.

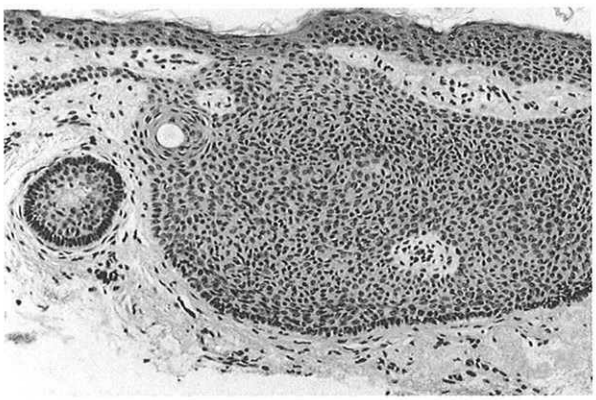

Fig. 5: Tumour of follicular infundibulum. A plate of light staining outer root sheath epithelium is formed in connection with the lower surface of the epidermis. H&E. X-125.

We selected the term "organoid nevus" over nevus sebaceous to stress the complex nature of this lesion that involves malformation of the entire skin rather than only the sebaceous glands.[30] Organoid nevi are usually present at birth and in their most common location on the scalp are characterized by a plaque of alopecia. In this infantile stage, the epidermis may be

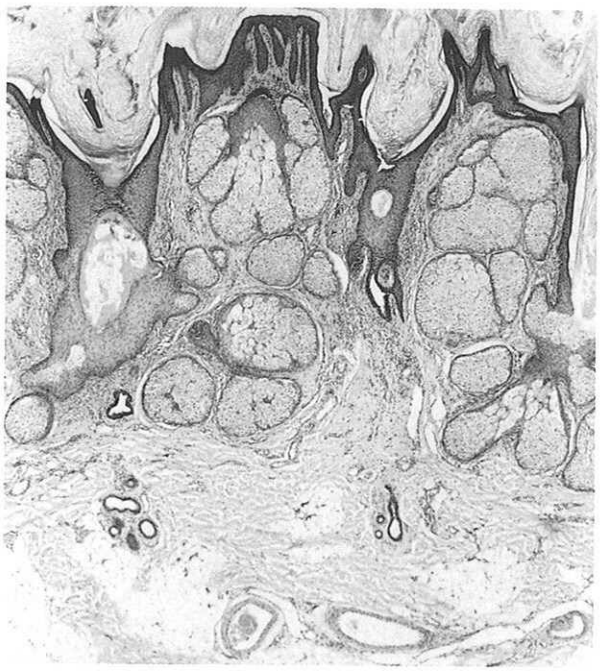

Fig. 6: Organoid nevus (nevus sebaceous). In addition to verrucous epidermal thickening and sebaceous hyperplasia, this scalp lesion shows absence of hair follicles and the presence of ectropic apocrine glands. All cutaneous sructures are abnormal in this nevoid malformation. H&E. X-25

acanthotic. The pilosebaceous structures are incompletely formed and the apocrine glands are not yet recognizable. The second stage, usually during the adolescence, is characterized by rapid increase in thicknss of the lesion which may show a yellowish, smooth lobulated or brown verrucous hyperkeratotic surface. The lesion always remains hariless. The hairless nature may not be appreciated in facial lesions and if the lesion is of a central facial location, it may be associated with the central nervous system, musculoskeletal and ophthalmic abnormalities as part of a syndrome. At this stage (Fig. 6) now the presence of large sebaceous glands may justify designation to nevus sebaceous. However, one has also to recognize that the hair follicles remain abnormally formed and primordial and the ectopic apocrine glands are

now recognized in more than 50% of the cases. The adult stage of organoid nevus is characterized by development of various benign and malignant adnexal neoplasms within the nevoid malformation. Syringocystadenoma papilliferum and basal cell epithelioma are the most common superimposed lesions but almost any other adnexal tumours may appear. Malignant lesions include apocrine carcinomas, undifferentiated adnexal carcinomas and squamous cell carcinoma.

A case with "epidermotropic eccrine carcinoma" was reported and the subject of eccrine adenocarcinoma was again discussed in a review of 35 cases classified into five categories including eccrine porocarcinoma, syringoid (adenoid cystic) eccrine carcinoma, clear cell eccrine carcinoma, mucinous eccrine carcinoma and the more recently recognized microcystic eccrine carcinoma. [31,32]

Histopathology of palmar pits in basal cell carcinoma syndrome was studied with Dr. James Howell.[33] It was shown that the defect is secondary to abnormal keratinization in a well-defined area. In this area, the epidermal basal cells remain undifferentiated and do not keratinize normally. The epidermal rete ridges are populated with small basaloid cells, a situation similar to that of a basal cell epithelioma. In rare occasions, basal cell epithelioma may develop within the palmar lesions.

Apocrine cystadenoma was interesting because of the clinical pigmentation giving an impression of a blue nevus or malignant melanoma.[34] The cystic structures of this lesion are lined in part with sweat ductal and partly with high columnar apocrine-type secretory epithelium. The pigment is lipochrome. Inflammatory linear varrucous epidermal nevus is characterized clinical by linear lesions that appear inflammatory and dermatitic.[35] Histologically shows alternating areas of orthokeratosis and parakeratosis over a generally acanthotic epidermis.

Pilar sheath acanthoma is usually solitary, facial with the upper lip as the most common location.[36] Clinically it resembles a dilated pore. Histologically it shows a central cystic dilated hair follicle surrounded with massive proliferation of the outer root sheath epithelium that extends outward in all directions.

The latest entity in the class of adnexal tumours is basaloid follicular hamartoma that occurs in localized, linear unilateral or generalized forms.[37,38] The localized lesions show a plaque of alopecia. The linear unilateral form resembles a systematized epidermal nevus. The generalized form shows diffuse papular lesions and alopecia. Histologically, (Fig. 7) individual hair follicles are transformed into a basaloid hamartoma that may resemble a miniature premalignant fibroepithelial tumour or miniature trichoepithelioma.

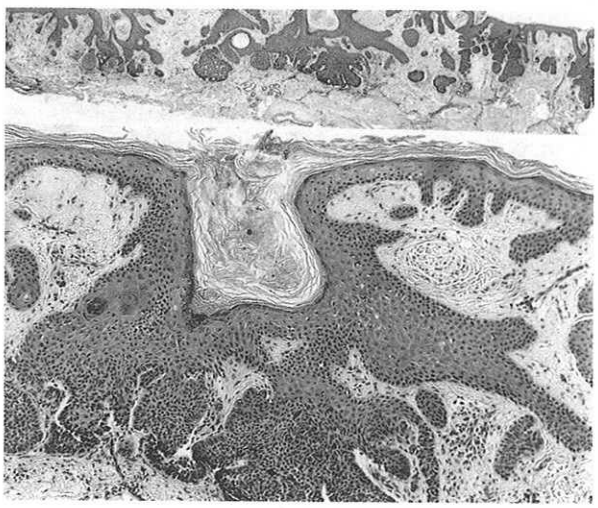

Fig. 7: Basaloid follicular hamartoma. A localized lesion shows a field of skin in which all the hair follicles are transformed into microscopic neoplasms resembling miniature trichoepitheliomas. H&E. X-25 and X-125.

Epithelioid cell histiocytoma is a lesion that comes as a differential diagnosis of intradermal Spitz nevus.[39] The epidermis overlying this class of histiocytoma may be normal or slightly acanthotic. The dermis

shows massive proliferation of epithelioid cells individually or in small clusters. Giant cells are not prominent and small collections of lymphocytes are present. Immunostaining shows positive reaction for vimentin, alpha-1-antitrypsin and common leukocyte antigen. Stains for S-100 protein and HMB-45 were negative. We have remained open-minded in the controversies concerning dysplastic nevi. Initially, we published a series of sporadic cases with no family history of similar lesions.[40] Latger, histopathology of dysplastic nevi was further investigated in a large series of consecutive cases. [41]

Individuals with dysplastic nevi have many moles of different sizes. Their pigmented nevi show irregular border and variation in colour. The majority of the lesions are histologically junction or compound nevi. The epidermis shows elongated rete ridges that may join each other and exhibit lentiginous melanocytic hyperplasia. Junctional nests (Fig. 8) are irregularly spaced, may be elongated parallel to the surface in connection with several epidermal rete ridges and are often populated with cells having abundant clear cyptoplasm or with dust-like pigment granules. The papillary dermis shows laminated fibroplasia, pigmented macrophages and lymphocytic infiltrate. The intradermal nests are usually populated with small melanocytes having round or ovoid nuclei and scanty cytoplasm. Dysplastic nevi occur in 2-8% of the U.S. population and may be associated with a 10% risk of developing malignant melanoma. Lifetime risk of malignant melanoma at this time in the U.S. population is 1%. Those with positive family history or dysplastic nevi syndrome, however, may have a 100% lifetime risk of malignant melanoma if two or more family members already have malignant melanoma.

A recent publication in the Journal Caner, 1993 was concerned with malignant melanoma in childhood.[42] Aproximately 30,000 cases of malignant melanoma occurs in the United States each year. Malignant melanoma is a

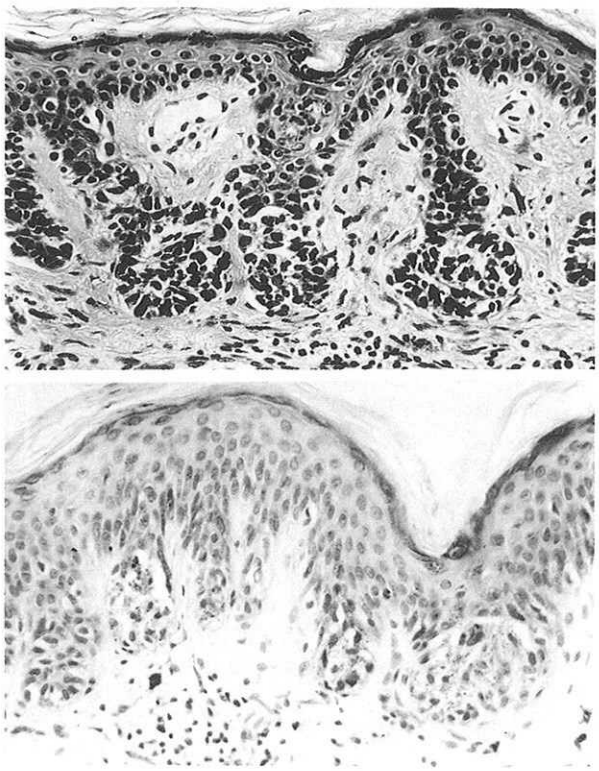

Fig. 8: Dysplastic nevus. Upper shows elongation of the epidermal rete ridges and junctional nests. H&E. X-225. Lower shows the junctional nests populated with melanocytes having abundant and dust-like pigment granules. Note the absence of upward transformation of melanocytic cells within the overlying epidermis. H&E. X-225.

disease of adults. Malignant melanoma in childhood is extremely rare. A review of the records in our laboratory within a period of 32 years and among 850,000 consecutive skin biopsy specimens showed 7,620 cases with malignant melanoma. Six of these occurred in children 14 years of age and younger. Three of these were initially diagnosed in our laboratory and three others were seen in consultation from other institutions.

Rarity and certain histologic peculiarities make diagnosis of malignant melanoma in childhood very difficult. Two histologic features that hallmark malignant melanoma in adults are not significant in children. We

learned that large congenital nevi in newborns may show significant junctional activity with nests of large cells and some upward transmigration as a normal component. We also learned that in the newborn lesions, mitotic figures may be found within the intradermal nests as much as 3 to 5 per high power field, a process that will gradually subside. We noted that junction nevi in children when over the acral skin areas may exhibit pagetoid epidermal involvement by upward transmigrating melanocytes. We learned that infants with large congenital nevi may develop nodular lesions made up of proliferation of richly vascular and edematous connective tissue, elongated fibroblasts and collections of melanocytes that may give the false impression of a malignant lesions.

We found that malignant melanoma in childhood may occur in seven different clinical settings. Our six cases included one congenital with leptomeningeal melanoma, one developing in congenital nevus, one in a child with dysplastic nevi, one with primary nodular malignant melanoma and two classified as malignant Spitz nevi.

The balance sheets for the past 35 years include examination of approximately one million skin biopsies, over 200 scientific publications, 10 textbooks and training of 17 fellows. Dermatopathology provided me with an opportunity to travel to many beautiful lands, to meet and develop friendship with many colleagues.

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