

MECHANISM OF RECURRENCE OF PIGMENTED NEVI FOLLOWING DERMABRASION

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Abstract. A study was made of pigment freckles which recur after skin abrasion of spotted grouped pigmented nevi, according to the lapse of time, chiefly by means of the fluorescence method of Falck and Hillarp. The mechanism of recurrence is summarized as follows. Nearly simultaneously with the epidermal regeneration, dendritic melanin-producing cells derived from hair follicles and eccrine sweat ducts appear in the basal and prickle-cell layers of epidermis. These cells then create junction activity in the basal layer of epidermis, in the hair follicles and in the eccrine sweat duct walls. Finally, these nevus cells drop off into the underlying layer of scar tissue along the epidermal appendages. The dendritic melanin-producing cells seen in the early regenerative pigment freckles were thought to be incompletely differentiated nevus cells in the pre-stage of junction nevus formation. Appearance of dendritic melanin-producing cells and formation of junction activity in the eccrine sweat duct walls suggest the following possibilities. (1) In the cases of spotted grouped pigmented nevus which we studied, nevus cell proliferation also occurred eccrine-centrally on pathogenesis. (2) An important role is played by the eccrine sweat ducts in the recurrence of ordinary pigmented nevi after incomplete removal. (3) Eccrine-centered nevus cells are derived from nevoclasts in the eccrine sweat duct walls.

Key words: Pigmented nevus; Fluorescence method; Sweat duct, eccrine; Dermabrasion; Melanin-producing cells, dendritic

In Japan, pigmented nevi are usually treated, according to the size and location of the lesion, with excision, electrocautery, cryotherapy with solid carbon dioxide, dermabrasion, skin grafting and so on. Except in the case of complete excision, these procedures may often be followed by recurrence. Pigment freckles which recur after incomplete removal of pigmented nevi are known to represent junction nevi histopathologically. The origin of junction nevus cells seen in the regenerating epidermis has not yet been clarified. Schoenfeld & Pinkus

(9) and Vezekenyi & Nagy (10) stated that junction nevus cells are derived from the margin as well as from the remnant hair follicles of the original lesion.

Cox & Walton (2) assumed that the residual dermal nevus has some influence upon the formation of junction nevus, though the epidermal nevus cells and the persistent intradermal nevus cells are separated from each other by the scar tissue.

The main purpose of this research is to study in detail the mechanism of recurrence of pigmented nevi after skin abrasion, especially to study the morphological characteristics and the origin of nevus cells in the pre-stage of junction nevus formation.

MATERIALS AND METHODS

The peculiar type of pigmented nevus composed of a grouping of black to blackish brown papules or freckles on various-sized brown pigment spots is called "spotted grouped pigmented nevus" in Japan. Recently we found that spotted grouped pigmented nevus can be classified into 3 types (7). Our study is concerned with 7 cases of this pigmented nevus after skin abrasion (5 cases of type I and 2 cases of type II) [Table 1]. Though there are some differences clinically and histopathologically between types I and II, pigment freckles which recur after dermabrasion run nearly the same clinical course. For the purpose of treatment and histopathological study, the central portions of these lesions were excised and the remaining areas were planed totally or partially to the depth where visible pigment was almost entirely removed. The clinical course of these nevi after skin planing shows a uniform pattern. Three to four weeks after the skin planing, nearly simultaneously with the completion of epidermization, pigment dots which are sometimes follicularly localized appear and gradually increase in number. Three to four months postoperatively, these pigment dots coalesce to form a diffuse black pigment spot corresponding to the dermabraded area. Such a pigment spot gradually fades with the lapse of time and changes again into the former dot-like pigment freckles. On the scars present in these

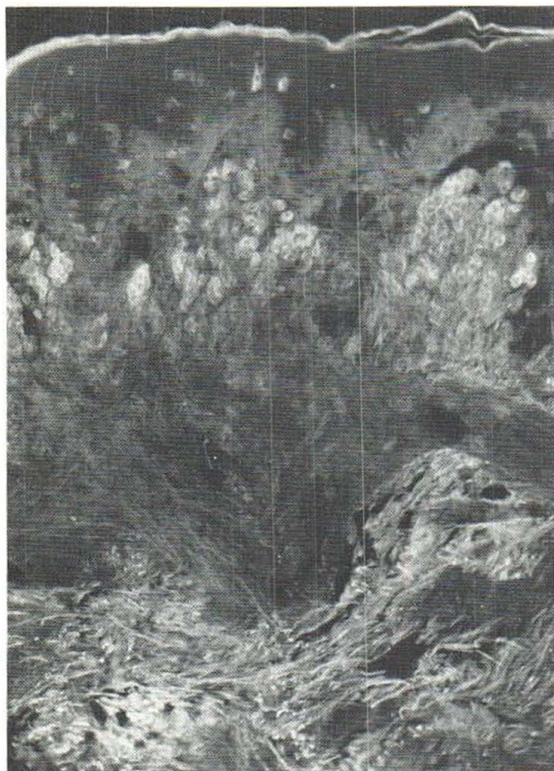


Fig. 1. Histopathological finding of spotted grouped pigmented nevus before dermabrasion. Dendritic melanin-producing cells are observed in the basal layer of epidermis, and nevus cells located in the upper dermis emit specific fluorescence in the yellowish-green to yellow range. Autofluorescence of elastic fibers is prominent in the lower dermis (fluorescence method, original magnification $\times 45$).

nevi after excision, regenerative pigment freckles were sometimes observed. According to the size of the lesions, these regenerative freckles were excised 1 to 3 times; 3~4 weeks, 3~4 months, and 12~15 months after the initial procedure.

The tissue specimens taken from these lesions were divided into three groups. The first group specimens were fixed in 10% formalin and stained with hematoxylin-eosin, Masson-silver, and Weigert-van Gieson. The second group of specimens were cut in a cryostat and studied on dopa reaction. The third group of specimens were frozen in dry ice-cooled isopentanol immediately after excision, freeze-dried for 7 days and treated with formaldehyde vapour at 80°C for 1 hour. After paraffin embedding, these specimens were sectioned horizontal or vertical to the skin surface at a thickness of 10~12 μm , and were mounted for fluorescence microscopy (6). In order to distinguish specific from non-specific fluorescence, the pieces of tissue were treated as mentioned above except for formaldehyde vapour. Thus treated, melanocytes usually emit green specific fluorescence, and nevus cells emit specific fluorescence within green to yellow range. These specific fluorescences are considered to denote the presence of dopa or dopa-containing compounds (1, 8).

RESULTS

1. Histopathological finding prior to dermabrasion of spotted grouped pigmented nevi

These nevi were intradermal nevi histologically except in case 6. Nevus cells facing the epidermis in the upper dermis and those surrounding the hair follicles and the eccrine sweat ducts, contain abundant melanin. These findings differ from those in eccrine-centered nevi described by Mishima (4). Fluorescence microscopy revealed the following findings in these nevi (Fig. 1). In the specimens not treated with formaldehyde, strong autofluorescence is emitted from the horny layer and the fibrillar structure of the dermis. Dendritic melanin-producing cells which emit green specific fluorescence were observed at the dermo-epidermal and dermo-follicular junctions more densely than in the normal skin, but were not observed in the eccrine sweat duct walls. Large epithelioid A-type nevus cells in

Table 1. Summary of data obtained in seven cases of spotted grouped pigmented nevus

Case	Age	Sex	Onset	Site	Clinical finding	Histopathological finding	Time of pathological exam. of recurrent pigment freckles
1	21	♂	At birth	Rt. buttock	Blackish papules	Intradermal nevus	3 wks. 3 mos. 12 mos
2	12	♀	At birth	Rt. buttock	with hairs grouped	Intradermal nevus	1 mo. 3 mos
3	19	♂	At birth	Rt. loin	on a brown pigment spot (type I)	Intradermal nevus	8 mos
4	31	♂	At birth	Rt. leg		Intradermal nevus	15 mos
5	37	♀	At birth	Rt. thigh		Intradermal nevus	3 mos
6	4	♂	At birth	Rt. chest	Blackish freckles	Compound nevus	4 mos
7	6	♀	At birth	Lt. leg	without hairs grouped on a brown pigment spot (type II)	Intradermal nevus	3 wks. 3 mos

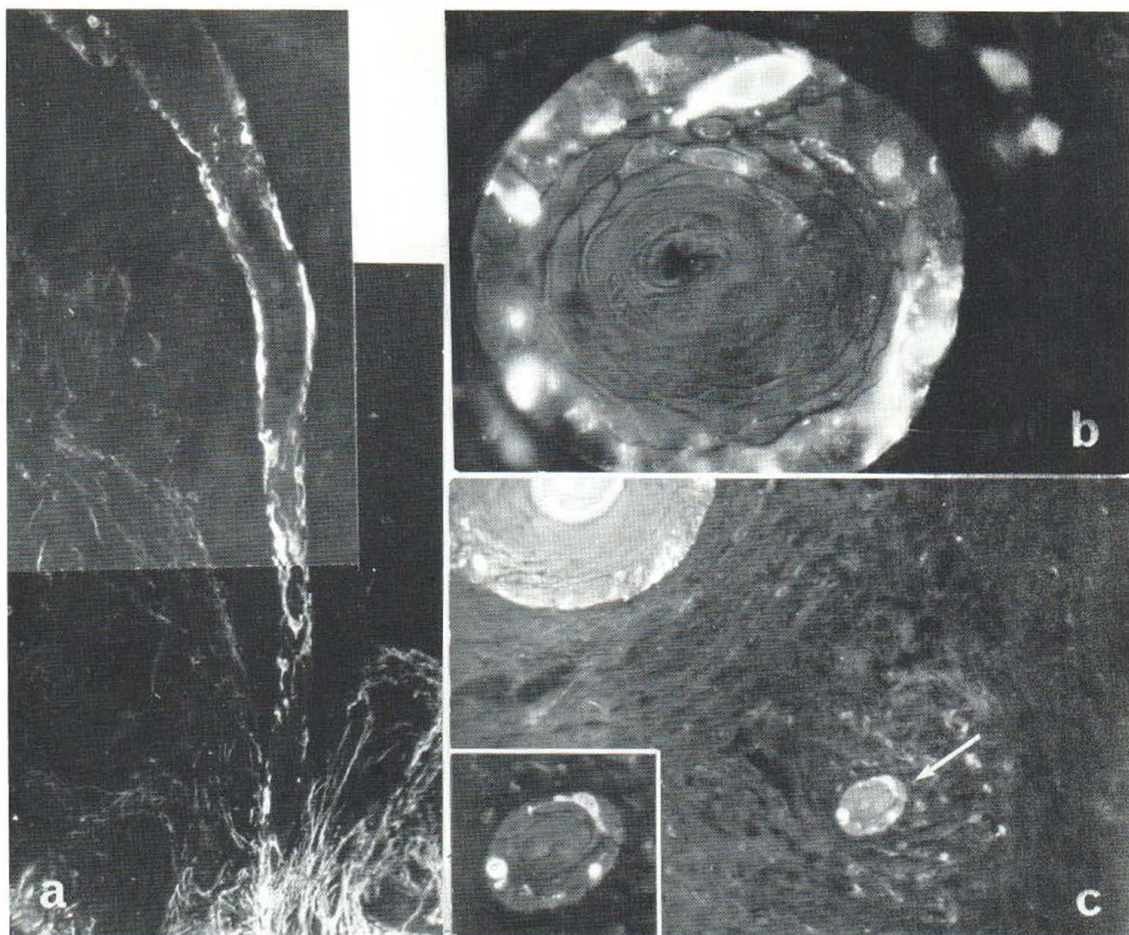


Fig. 2. Histopathological finding of regenerative pigment spot 3 weeks after operation. In the vertical (a) and horizontal (b, c) sections, dendritic melanin-producing cells are seen in the regenerative eccrine sweat duct walls. These cells are dense in the outermost layer of the sweat ducts composed of several layers just beneath the epider-

mis, and dense or sparse in the outer layer of the double-layered sweat duct in the dermis. Inset in (c) represents a higher magnification of the portion indicated by arrow (fluorescence method, (a, c) Original magnification $\times 50$; (b) original magnification, $\times 75$).

the upper dermis have an intense yellowish-green to yellow specific fluorescence. No elastic fibers are observed in between these cells. Green specific fluorescence emitted by small, round B-type nevus cells which are situated in the middle to deep dermis gradually diminishes and is finally lost as the nevus cells pass downwards, and autofluorescence of elastic fibers becomes distinct.

2. Chronological observation of recurrent lesions following dermabrasion of spotted grouped pigmented nevi

(a) *Recurrent lesions 3 to 4 weeks after operation.* Nevus cell nests remain almost unchanged in the

middle to deep dermis. These nevus cell nests have neither specific fluorescence nor melanin, but abundant elastic fibers are to be observed in them. They are covered by a layer of fibrous scar tissue which appears dark under the fluorescence microscope, due to a lack of elastic fibers; regenerative collagen fibers do not emit autofluorescence. This scar tissue is covered by regenerative epidermis. Many large dendritic melanin-producing cells, which are strongly dopa-positive, rich in melanin in Masson silver staining and emit yellowish-green to yellow specific fluorescence by the fluorescence technique, are observed chiefly in the basal-cell layer—and at times in the prickle-cell layer—of the epider-

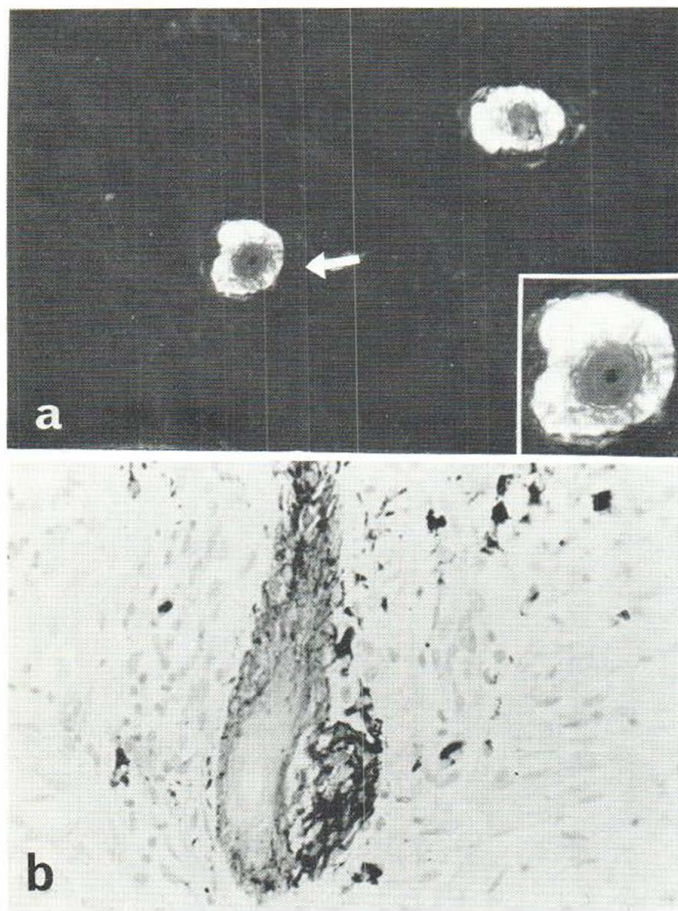


Fig. 3. Histopathological finding of regenerative pigment spot 3~4 months after operation. Junction activity is formed in the eccrine sweat duct walls (*a, b*). Inset in (*a*) represents higher magnification of the portion indicated by arrow. (*a*) Fluorescence method; (*b*) Masson-silver stain, original magnification $\times 30$ respectively.

mis and the infundibular portions of hair follicles. There is no evidence of malignancy in these cells. It is remarkable that these cells are observed in the eccrine sweat duct walls. In vertical (Fig. 2*a*) and horizontal sections (Fig. 2*b, c*), dendritic melanin-producing cells in the sweat duct walls are dense in the outermost layer of sweat ducts composed of several cell layers just beneath the epidermis, dense or sparse in the outer layer of sweat ducts composed of two cell layers in the dermis, and not observed at all in the sweat ducts penetrating the remaining nevus cell nests in the dermis, nor in the secretory portions.

(*b*) *Recurrent lesions 3~4 months after operation.* The nevus cells in the middle to lower dermis surrounded by scar tissue show no signs of activity. Dendritic melanin-producing cells are observed abundantly in the basal layer of the epidermis and sparsely in the prickle-cell layer. Most of these cells have indistinct dendritic processes and have a tend-

ency to grouping. Such a finding is presumed to correspond to junction activity. These junction activities were observed at the dermo-epidermal and dermo-follicular junctions, and in the intra-epidermal and upper intradermal portions of eccrine sweat ducts (Fig. 3*a, b*). Dropping off of the nevus cells from the junctional components into the scar tissue is exceptional.

(*c*) *Recurrent lesions 12~15 months after operation.* Dendritic melanin-producing cells are observed in the elongated rete ridges, infundibular portions of hair follicles, and intra-epidermal and intradermal portions of eccrine sweat ducts. Junctional activity and dropping off of the nevus cells into the scar tissue are not observed. However, the nevus cells which are located under the scar tissue and face the hair follicles and eccrine sweat ducts emit yellowish-green specific fluorescence and have abundant melanin (Fig. 4). No elastic fibers are found in between these cells. On the other hand,

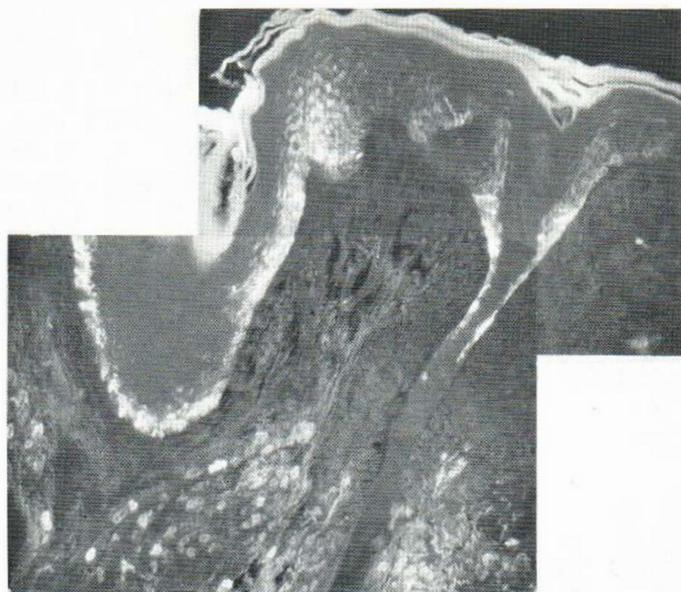


Fig. 4. Histopathological finding of regenerative pigment spot 15 months after operation. Dendritic melanin-producing cells are seen in the hair follicles and eccrine sweat duct walls. Specific fluorescence is observed in the nevus cells which are located under the scar tissues and face the hair follicles and eccrine sweat ducts (fluorescence method, original magnification $\times 30$).

the remaining nevus cell nests into which no epidermal appendages run lack specific fluorescence and melanin, and the autofluorescence of elastic fibers is prominent.

(d) *Recurrent lesions on the scar after operation.* In order to further clarify the relationship between the dendritic melanin-producing cells and the epidermal appendages, comparative studies were made on the scars existing in the nevi with/without regenerative pigment freckles. In the scar without pigment freckles, the whole dermis is replaced by fibrous scar tissue, and no nevus cells or epidermal appendages are observed therein. In the basal layer of epidermis, there is little melanin and few melanocytes, in comparison with normal skin. In the scar with pigment freckles, the melanin in the epidermis is increased and many dendritic melanin-producing cells are found, chiefly in the basal layer of the epidermis. No nevus cells are found in the scar tissue. However, there were observed eccrine sweat ducts which led from the nevus cell nests in the lower dermis surrounding the scar tissue to the regenerative epidermis (Fig. 5). This finding suggests the possibility that the dendritic melanin-producing cells originate from the epidermal appendages.

DISCUSSION

It is a well-known fact that pigmented nevi originate from junction nevi and develop into intradermal

nevi via compound nevi. However, the morphology of nevus cells in the pre-stage of junction nevus formation is not at all well known. Recurrence of pigment nevi after incomplete removal is thought to arise histopathologically from junction nevus formation (2, 9, 10). Such a change is understood as nevus cells' reliving of the early part of their natural history (9). Many dendritic melanin-producing cells, which were observed solitarily in the epidermis and in the epidermal appendages of the pigment freckles recurring 3–4 weeks postoperatively, lose

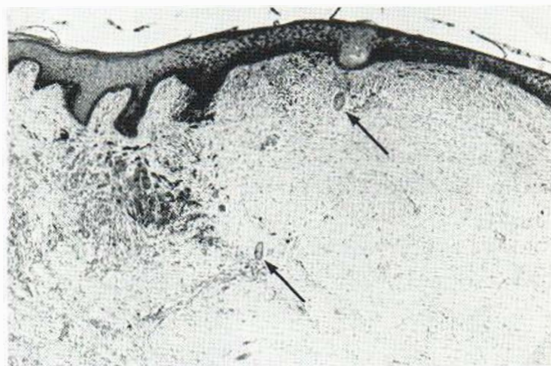


Fig. 5. Histopathological finding of regenerative pigment spot on the scar after excision. The epidermis is rich in melanin and regenerative eccrine sweat ducts (arrows) are seen which lead from the neighbouring nevus cell nests to the epidermis overlying the scar (Masson-silver, original magnification $\times 20$).

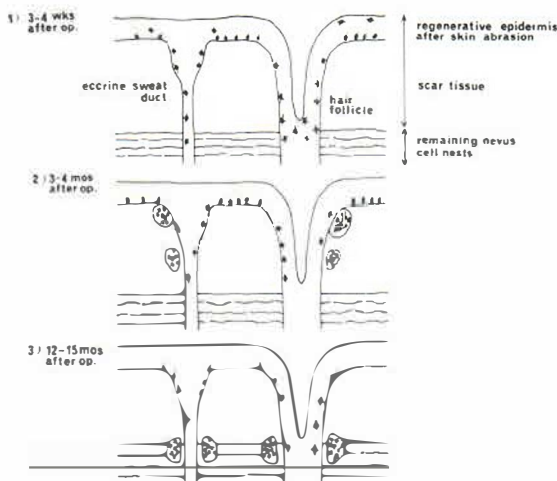


Fig. 6. Mechanism of recurrence of spotted grouped pigmented nevus.

their dendritic processes 3~4 months after the operation and create junctional activity. Such dendritic melanin-producing cells are larger than melanocytes in the normal skin and emit yellowish-green to yellow specific fluorescence as do nevus cells located at the dermo-epidermal junction and in the upper dermis. Such a finding suggests that these dendritic melanin-producing cells play an important role in junction nevus formation. In other words, nevus cells in the pre-stage of junction nevus formation are thought to have dendritic processes morphologically.

From what portion of a pigmented nevus do dendritic melanin-producing cells originate and what course do they take to approach the epidermis? Two hypotheses have hitherto been discussed concerning the origin of nevus cells seen in the regenerating epidermis following incomplete removal of pigmented nevi (3). In one hypothesis, nevus cells are assumed to be derived from the nevus cells present in the margin of the lesion, and in the other hypothesis, from the nevus cells remaining in the deep dermis. The following fact observed in our study suggests that dendritic melanin-producing cells are derived from hair follicles and eccrine sweat ducts; that is to say, the recurrent pigment freckles are not formed from the margin of the lesion toward the center clinically, but appear as dots within the lesion; the comparative study on scars with/without the recurrent pigment freckles suggests a close relation between the formation of recurrent pigment freckles on the scar and regenera-

tion of the epidermal appendages in the scar tissue. Concerning the source of dendritic melanin-producing cells, however, it is obscure whether they are inactively pre-existent in the epidermal appendages or whether they are derived from the undifferentiated cells of neural crest origin present in the remaining nevus cell nests.

In 1970 Mishima studied 3 cases of spotted grouped pigmented nevus histopathologically and found that the spotted pigmentation to be observed clinically is a change based on eccrine sweat duct-centered proliferation of nevus cells, and in 1973 he proposed the term eccrine-centered nevus (4). In 1971, Yoshinaga et al. (12) studied 18 cases of this nevus histopathologically, and reported that the nevus cell proliferation was eccrine-centered in 10 cases, but no association was noted between the nevus cells and skin appendages in the remaining cases. This fact suggests a possibility that there are different types in this disease.

Recently we classified spotted grouped pigmented nevus into 3 types on the basis of results obtained in a clinical and histopathological study of 16 cases of this nevus (7). The histopathological finding obtained in our study on spotted grouped pigmented nevus differs from Mishima's description. However, the appearance of dendritic melanin-producing cells and the formation of junctional activity in the eccrine sweat duct walls of the regenerating pigment freckles suggests the following possibilities. 1) In the cases of spotted grouped pigmented nevus which we studied, growth of nevus cells also occurred eccrine-centrally on pathogenesis. 2) concerning the recurrence of ordinary pigmented nevi after incomplete removal, eccrine sweat ducts play an important role, and 3) the origin of eccrine-centered nevus cells is derived from nevoclasts in eccrine sweat duct walls.

A possibility that malignant melanoma develops on a pigment nevus after incomplete removal is generally denied (2, 9, 11). The finding that recurrent pigment freckles 3~4 months after operation assumed a diffuse blackish color, in contrast clinically to the original lesion, and a finding that melanin-producing cells were observed on histopathological examination in the prickle-cell layer of epidermis, both led us to a suspicion of malignant change. However, the following fact allayed this suspicion. There is no evidence of malignancy, histopathologically, of these melanin-producing cells. Clinically, the recurrent blackish pigment

spot is localized only in the abraded area, and fades with the lapse of time. The melanin-producing cells in the prickle-cell layer of epidermis were observed by Mishima & Widlan (5) in the epidermis and hair follicles of embryos.

From the above results, the mechanism of recurrence of spotted grouped pigmented nevi after incomplete removal is summarized as follows (Fig. 6). Simultaneously with the epidermal regeneration, dendritic melanin-producing cells derived from hair follicles as well as from eccrine sweat ducts appear in the basal and prickle-cell layers of the epidermis. These cells then, come together at the basal layer of epidermis, hair follicles and eccrine sweat duct walls, lose their dendritic processes, and form junctional activity. Finally, these nevus cells drop off into tissue beneath the scar, along the epidermal appendages.

ACKNOWLEDGEMENT

The details of this study were published by Imagawa, one of the present authors, in *Jap J Derm* 84: 273, 1974 (in Japanese).

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Received September 8, 1975

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