Studies on Melanin.

VII. Mongolian Spot Cell and Blue Nevus Cell.

By

Minor Ito.

(From the Department of Dermatology, Faculty of Medicine, Tohoku University, Sendai. Director: Prof. M. Ito.)

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In contrast with black or brown color tone of pigmented nevi, there are two kinds of congenital deep blue pigmented spots: mongolian spot and blue nevus. The former appears generally on sacral region of newborn and fades within several years, while the latter appears anywhere but is comparatively seldom and exists for life. These two nevi resemble each other in the point that they are both due to the melanophore of deeper dermal layer. Their difference and entity have also been studied at various times, although we have not come to a definite conclusion as yet.

I1) studied formerly the so-called nevus cell of pigmented nevi and described the theory of neuroectodermal origin. In this article I intend to investigate the genesis of mongolian spot and blue nevus by means of methods similar to that referred to in my former article: principally Bielschowsky-Seto’s neurofibril staining and Bielschowsky-Maresch’s Gitterfaser staining were used.

Results of Investigations.

1. Mongolian spot. The results of investigations of the sections taken from 11 cases of fetal six to three months corpses and one case of two months living body, are similar to the description given by my predecessors. In other words, I indicated the mongolian spot cell in lower half layer of derma as fusiform, oval, stellate or somewhat elongated string-like melanophores lying along the paths of connective tissue and with their pigment granules greater and denser than those of the basal layer of epidermis. They are so filled with pigment granules that we can hardly distinguish their nuclei. These pigment granules do not fade by hydrogen peroxide procedure. In my examination of peroxydase in a section taken from living body by Okano-C method, I found peroxydase positive granules among the black granules of melanin. This suggests that there is some relation-
ship between this and the positive data of dopa-reaction by Bloch-Bahrawy. Then I examined closely the arrangement of these chromatophores and found that although most of them exist parallel to cutaneous surface, not all coincide with the paths of connective tissues, but some come in contact with small blood vessels; some are joint with their cellular processes; some twist with blood vessels like a gabion. We can often see chromatophores near small bundle of neurofibril and a little more of them at places where blood vessel and neurofibril cross each other. But the conglomeration or proliferation of chromatophores with abnormal ramification and winding of cutaneous nerve fiber as its center, such as I found in my previous report on nevus cell, can not be seen anywhere. Moreover, no figure suggesting transition to Schwann's cell or nothing like an endoneural apparatus (Fibres naeviques, Lames foliacées) specially mentioned by Masson, is seen. The mongolian spot cells exist next to ductus sudoriferus or can be seen around arrector muscle but are rarely seen near sebaceous gland and hair follicle.

On the Gitterfaser staining slides, I found the above mentioned figure of chromatophores around blood vessel packed within argentaffin fibril and another figure closely connected to argentaffin fibril in subcutaneous adipose tissue, but with regards to mongolian spot cells in connective tissue I could not ascertain its relationship to argentaffin fibril. Only in preparation of six months fetus, big stellate or oval chromatophores are found plentifully in the part where collagenic fiber is rare and argentaffin fiber abundant. I could not discover in every case the inlaying figure of each cell into each reticulum, which means that the mongolian spot cell may have some partial relationship to reticulum tissue and may be partly connected with the so-called precollagenic argentaffin fibril in its embryonal stage.

2. Blue nevus. The first case, 18 years old female, has light blue rice corn sized nevus on her forearm; the second case, 64 years old male, has indigo blue horse bean sized nevus on his hairy head; and the third case, 21 years old female has deep blue nevus on her buttock. Results of examinations of these cases are as follows: the first case has a small amount of chromatophores scattered horizontally in connective tissue below the middle layer of the derma, and in contact with blood vessels there are some in fusiform and stellate. Therefore, we can not distinguish them from mongolian spot cells. However, latter two cases are abundant with chromatophores and this coinsides with the description of Tièche, Sato and Imschentzky. These chromatophores run together with collagenic fiber in the range from the middle layer of derma to the deeper layer and they look like a bundle as a whole located horizontally in stratum reticulare and obliquely or vertically in subcutaneous adipose tissue. In case their black granules are dense, the neighbouring parts look like black fiber, and in case they are scarce, we can see their nuclei in their centers. These
chromatophores are found coincidentally in or among diffused collagenic fibers. Most part of these collagenic fibers show purplish red metachromasia by Mallory's staining. This may be presumably a sort of degeneration of collagenic fibers induced by the specific biological status of tissues containing chromatophores. There are stellate, fusiform, comma-shaped and, rarely, ovoidal chromatophores among or near fibrous chromatophore bundle (above mentioned) and their black granules are rather large. But chromatophores which have small granules show oval nuclei. Moreover, I found in my preparations small amount of large stellate immature form which had been found by Imschentzky in derma of monkey but not in blue nevus. Stellate and fusiform chromatophores are shown in contact with blood vessel or ductus sudoriferus and sweat gland. The elastic fiber disappears almost completely in parts where fibriform chromatophores are densely located and at the layer above them.

The relationship between neurofibril bundles and melanophores studied by Bielschowsky-Seto's staining is quite different from that of nevus cells. The clearly demarcated cross-sections of neurofibrils (N) are indicated among groups of fibrous melanophores and there is no figure suggesting affinity between neurofibrils and melanophores. Moreover, that neurofibril is slightly lighter stained and has less amount of Schwann's nuclei than other neurofibril found apart from chromatophore nest. These characteristics are suggestive of embryonal unripe neurofibril (Fig. 1).

By Bielschowsky-Maresch's staining in part where fibrous chromatophores are densely located we can hardly distinguish Gitterfaser, but ar-
gentaffin fibril (stained fresh blue by Mallory's method) is easily distinguished in parts where stellate chromatophores gather together. But all of these cells are not packed within argentaffin reticulum. The stellate processes of some of these cells look like an argentaffin fibril because of these dense argentaffin granules. In the circumference of small blood vessels, however, melanophores are packed distinctly in reticulum tissue. The clearly demarcated neurofibril among melanophore groups is lighter stained and the author believes this to be an embryonic unripe neurofibril according to the results of previous neurofibril staining. However such belief is not conclusive in view of the labil character of silver impregnation method.

The biochemical characteristics of the pigment contained in chromatophores are as follows: ferrous reaction is negative, silver reaction positive, therefore it is assumed to belong to melanin. Faints slightly with hydrogen peroxide, especially the pigment in stellate type chromatophores has stronger resistensy than that of fibrous type one and remain unchanged even by hydrogen peroxide procedure of one week duration (daily exchange of hydrogen peroxide). Thus according to the above mentioned characteristics and the fact of the simultaneous existence of positive and negative cells against dopa reaction (Sato and Stranz), it seems that there are several stages of chromatophores of blue nevus with regards to the morphological and biochemical character and especially in connection with the attitude of oxidation-reduction. Kreibich reported the existence of lipoid in 1 case of blue nevus which, however, I was unable to confirm by sudan III staining.

Summary of aforesaid observation is as follows: in the comparative study of the characteristics of melanophores between mongolian spot and blue nevus, I recognized exact homology concerning the morphology, location, disposition and biochemical attitudes (non-faintness with hydrogen peroxide and positive dopa reaction) and especially the relationship between neurofibril and chromatophore which I examined very closely, is quite different from that of nevus cells (previously reported). There is no affinity between chromatophore and neurofibril. On account of this definite distinction, mongolian spot and blue nevus coinside and both of them show pigment cell nests which are partly packed within reticulum tissue or diffused nests against argentaffin fibril. Yamamoto reported that as he found no transition between these two pathological hyperpigmentations he could not decide definitely that they were of the same species. But the first case of my blue nevus preparation can be considered to be the evidence of histological transition and, therefore, I believe these two pathological hyperpigmentations are essentially due to the almost homogenetic chromatophores.
About the origin of the mongolian spot cell, Bälz visualized the epidermal origin but the mesenchymal theory of Adachi was universally accepted. Kawamura, Kiyono, Katsunuma and others advocated the histiocytic theory and surmised that this is organically homologous but functionally different from the so-called chromatophores. Especially the cutaneous pigment of the monkey was minutely studied comparative-anatomically by Adachi and more recently by Imschentzky. They indicated the existence of dermal melanoblast in deeper layer against superficial so-called chromatophore, and emphasized that this is of the same species to which mongolian spot cell belongs. The difference between these two is merely that the pigment of the monkey is reciprocal proportionally in epidermis and derma. In other words, when it is abundant in epidermis, it is scarce in derma, while mongolian spot (dermal pigment) is prominent in colored races (epidermal pigment). The origin of chromatophores of blue nevus has been believed to be chiefly mesenchymal since the publication of Tièche. Imschentzky studied five cases of blue nevus and found it difficult to distinguish them from dermal melanoblasts of monkey. Although he could not notice in blue nevus the big stellate cell (unripe form) such as seen among monkeys, he made an interpretation that dermal melanoblast may be treated as a system sui generis.

As stated above, according to my observation, mongolian spot cell and blue nevus cell belong to the same species and they are different from nevus cell (reported previously) and, therefore, I definitely reject the ectodermal origin, and believe that is chromatophore of dermal origin as mentioned by Adachi and Imschentzky.

However, the problem, namely, from what kind of mesenchymal tissue the said chromatophore comes, can hardly be surmised. I also noticed in my observation of Bielschowsky-Maresch's staining, a view which suggests its relationship to reticulum tissue and in part unseparably mixed figure of chromatophore and argentaffin fibrils, thus I can not conclude hastely that such chromatophore originates indiscriminately from histiocyte or cell of reticulum tissue. What's more, silver impregnation belongs to an artificial procedure as in both neurofibril and Gitterfaser stainings and its labil character is universally known. Therefore, the entity of argentaffin fibril is still disputable, and on the other hand the extracellular protoplasma theory of Hueck, the tissue culture of Maximow, the biochemical experiment of Nageotte and other new knowledges appear one after another. In Japan, Sekine studied this recently, thus I think we can expect further development in this problem. The author refer only to the abnormality of congenital factor on one hand, and to the special biochemical status of
the foci on the other: the former, indicated by the co-existence of chromatophores and argentaffin fibrils, leads to the assumption of the remainder of so-called precollagenic argentaffin fibrils, while the latter are shown by the metachromasia of collagenic fibers in region abundant in chromatophores. So I want to reserve the problem as to its origin for the time being.

I can not overlook following facts: that Stranz\(^7\) observed contemporaneous existence of the so-called nevus cell in 3 out of 11 cases of blue nevus; that similar mixed existence of nevus cell was observed in 1 case each by Sato, Armuzzi, Dubreuilh\(^8\) and Petges. I think that foregoing cases are the associated cases of blue nevus and pigmented soft nevus because of the frequent instances of associated symptoms in many congenital abnormalities and the fact of the participation of both ectoderma and mesoderma observed in cases of phacomatosis. And I do not think this can be regarded as the data of epidermal theory of blue nevus.

**Conclusion.**

Mongolian spot cell and blue nevus cell belong to the same species and they are surmised to be the cells originated from mesoderma. Thus these are different from nevus cells of pigmented nevi which is neuro-ectodermal.

**References.**

2) Tièche, Virchows Arch., 1906, 186, 212.
3) Sato, Derm. W., 1921, 73, 1073.
4) Imschentzky, Arch. f. Derm., 1931, 162, 276.
6) Yamamoto, Arch. f. Derm., 1925, 149, 344.
7) Stranz, Arch. f. Derm., 1924, 147, 131.