VII. Nevus Fusco-caeruleus Ophthalmo-maxillaris Ota*

The nature of mole, pigmented nevus, blue nevus and Mongolian spot which belong to congenital melanosis had early been discussed and their pathogenesis had generally been made clear. But in 1939 Ota\(^1\) took notice of one special form among so-called pigmented nevi found especially on face and named it “Nevus fusco-caeruleus ophthalmo-maxillaris Ota.” Tanino\(^2\) stated its detailed clinical observation; in general, its typical case is unilateral, occupies the cutaneous distribution of the first or second branch of trigeminal nerve and is arranged diffusely as grouped ephelidelike spots in blue, brown and their middle tones and is often accompanied with melanosis bulbi. The origin of the pigment bearing cell, however, is not yet sufficiently explained and the recent supplemental reports in Japan limited to the casuistics. On the other hand, in the United States the differences between the similar cases to this nevus and blue nevus, Mongolian spot or argyria have been discussed. But its origin does not come to be investigated thoroughly at all. Therefore in the series of 110 cases of this disease at our department, I state first the clinical observations and in the second part present the histological and histochemical investigation.

Observation of Author's Own Cases

Before describing author's own cases I summarize Tanino's classification of his 26 cases; he classified as follows; 1) mild-, 2) moderate-, 3) intensive- and 4) bilateral-type. The mild orbital type is faint, the arrangement of pigmented spots is scattered and they are distributed over upper and lower palpebra, periocular and temple regions; mild zygomatic type is found between sulcus infralpebralis and sulcus nasolabialis and over zygomatic region. Moderate type distributes over the upper and lower palpebra, periocular, zygomatic region, cheek and temple, and about half of it invades radix and ala nasi also; intensive type spreads over besides above mentioned parts even to scalp (parietal and frontal region), forehead, brow, radix, ala and apex nasi; and bilateral type is the case in which abovementioned types are found on both sides. However, Sakurane\(^3\) reported the additional cases in which the pigmentation reaches to the distribution area of the third branch of trigeminal nerve (n. mandibularis), or to that of cervical or thoracic nerves. On the other hand, there is a type which is seen only at the apex and ala nasi or in the nostril.

I observed 106 cases among 110 in amount except 4 cases which were insufficient in clinical description. **Frequency:** From 1940 to 1950 the patients of this nevus amounted to 110 cases and all the dermatologic out-patients in this period were 27082, and its rate comes to 4.06% and this is 21.7% for congenital pigmented spot which appears on face.

**Sex:** Among 106 cases 22 were males and 84 were females. The decided

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* By Kunio Yoshida.
Nevus fusco-caruleus ophthalmo-maxillaris Ota

predominance of female, it appears, perhaps depends on the cosmetic complaint.

**Type:** Among 106 cases 45 were of mild orbital type, 22 were of mild zygomatic type, 19 were of moderate type, 10 were of intensive type (Plate VIII, Figure 30) 4 were of bilateral type, 3 were of each abortive and perinostril type, in brief mild type amounted to 2/3 of all cases.

**Location:** The lesion was most found at upper and lower palpebra and next found on the temple, zygomatic region, cheek, forehead, etc. In comparison with the cutaneous innervation, 18 cases were found only in the 1st branch region (n. ophthalmicus), 27 in the 2nd branch region (n. maxillaris), 55 extended to the both regions, and 1 extended to the whole region from 1st to the 3rd branch, 1 extended widely to the 3rd branch, the 3rd and 4th cervical nerve and the 2nd thoracic nerve, and 3 were only found at the apex, ala nasi and nostril. By the way, in 1 case which attacked both 2nd and 3rd branch regions pale blue pigmentation was also found on the buccal mucous membrane.

**Side of lesion:** 61 cases were on the right side, 39 on the left side and 6 cases were bilateral type. In comparing with type of lesion the difference between right and left side was scarcely found in the orbital type among mild type, but zygomatic moderate and intensive type are frequently found on the right side. From this it may be thought that there is any participation in the intrauterine position of fetus, but there is no significant difference between the 1st and 2nd attitude in the Japanese, so the factor which controls the side of lesion is not understood at all.

**Age of onset:** In 65 cases the lesion appeared by birth or soon after birth and 41 cases were the delayed-type. About half cases among them were mild orbital type, so it seems that there were many one who found the nevus late, and 4 cases in which one could not distinguish the nevus without the attention because it became considerable in each puberty, 1 case in which the pigmented nevus became remarkable after marriage, 6 cases in which the conditions such as contusion or collision, etc. motived the nevus. Thus I can't deny the fact that the embryonal terrain which grows very slowly is promoted or strengthened under the physical disharmony or some other inducement.

**Age of consultation:** Like common nevus many consult in infant and in puberty and patients from 1 to 2 years amounted to 21 cases, from 14 to 20 years 28, from 21 to 25 years 32, from 26 to 30 years 9, from 31 to 40 years 8 and from 3 to 13 years only 4 cases. According to the types of lesion patients who consulted in 1 or 2 years of age were 31.02% in moderate and intensive cases, while in mild cases they amounted to almost half, that is 16.4% and it seems natural on account of the cosmetic complaint that many patients of intensive type consult early in infancy.

**Color tone:** Color tone was generally spotted color which consists of ephelide-like brown and blue-nevuslike blue, and showed many tones of color, that is to say, black, blackpurple, blue black, deep blue, blue, fading blue, slate-blue, purplish brown, brown, and faint brown. This seems perhaps to depend on the healthy complexion and the quantity or the depth of pigmentation. The boundary was faint on account of fading in the periphery. These color tones scarcely changed after its perfection, but especially in female changes of the color tones were more or less seen according to the conditions such as menstruation or others. The observation of these changes was as follows; in 10 cases the color tone of whom became dark
during menstruation, 2 were the cases of fading, 2 were those of darkening when they became fatigued, each 1 case of seasonal darkening in summer and winter, and 3 cases showed the diurnal changes of color tone. By the way, this nevus was often found in one whose skin-color of face was darker for Japanese, and seldom in the women who had such snow-white complexion as seen in Tohoku district.

**Melanosis bulbi:** It was observed in 65 cases (61.3%) among the whole cases. Melanosis bulbi was found in the whole case in the intensive type, in moderate type 13 were found among 19, in the orbital type 28 among 45, that is, it is found in 2/3 cases, but in zygomatic type it was found only in 8 cases among 21. This melanosis bulbi was almost unilateral and was observed in accordance with the side of nevus, but in 6 cases found on both sides, and was only found on both sides in 1 case among the bilateral 4 cases, 2 cases was only found on the side high in the degree of pigmentation, and was not found in 1 case at all. The extent of melanosis bulbi varied between those in which the frontal surface of eye-bulb was almost blue in color to those in which the pigmentation was millet grain in size, while the color tone was also various from blue-black to brown and in the widely extended cases it is dark in blue and it becomes brown in proportion to the extent of spot.

**Inheritance:** In the observation of 106 cases, in 1 case each his mother and his cousin were also affected but the clear inheritance was not found. There was a patient whose mother had the blue nevus which is analogous disease to it and 14 cases in which the pigmented nevus was found in parents, children, brother and sister or relatives. There were two patients whose parents were consanguinously married.

**Histamine scratch test:** I determined the onset of erythema and wheal of 14 cases after linear scratching and instant application of 0.1% histamine chloride solution on both the nevus and healthy skin (see Table VII), 8 cases appeared earlier 4 simultaneously and 2 later on the nevus than the healthy skin and therefore the angioneurtotic disturbance of the nevus was observed in about half cases.

### Table VII

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age</th>
<th>Erythema</th>
<th>Wheal</th>
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<td>24</td>
<td>+30</td>
<td>+90</td>
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<td>F</td>
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<tr>
<td>F</td>
<td>29</td>
<td>0</td>
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Values in the table show the interval of erythema or wheal development on the nevus in seconds. (+) . . . sooner than, (-) . . . later than and (0) . . . simultaneous with erythema or wheal development on the normal skin.

**Diaphoretic test:** There was each one case in which the diaphoretic time of the nevus by the method of Wada was faster or later than the healthy skin, and I will hereafter pursue to investigate.

**Treatment:** Like the pigmented nevus, the carbon dioxide snow, rongalit
C or albalite C, were often applied, but in cases of highly developed lesion and being deep in blue color tone this treatment attacks the deeper layer of the nevus and leaves leucoderma or cicatrice, etc., and therefore it is difficult of cosmetic effect. I examined the alternative continual injection of vitamin C, adrenalin and adrenocortical hormone in turn in 15 cases and observed considerable effect in 6 cases, but in part of deep color tone the specially remarkable fading was not observed.

**Histological and Histochemical Observations**

24 out of 110 author's own cases were biopsied. Most specific alteration in the histological picture was seen in the corium; like Mongolian spot the pigment cells were seen most in upper reticular layer, next in middle layer and recognized in lower layer or about adipose tissue, and their sizes were various; the cells in comparatively upper layer are fusiform or stellate in shape and most of them became long string- or fiber-like cell as they go down to lower layer (Plate VIII, Figure 31). These very large cells became gradually slender in the periphery, and dendritic type cells were connecting with each other. Especially the pigment cells which were seen in adipose tissue were communicated with each other as if they embrace it. These pigment cells were seen sporadically in the cutis and some of them coming together, form such a bundle as was seen in blue nevus. Generally speaking, the long axis of the pigment cell was often parallel to the cutaneous surface and it was nearly accordant with the course of connective tissue, and intervened among fibers. But it arranged obliquely or vertically in the cells around small blood vessel, around sweat gland, sweat duct, sebaceous gland or among adipose tissue. The pigment granule which is the refractional melanin granule packed in these cells was much coarse in comparison to those of basal cell layer, and was so full in fusiform or stellate cell of upper layer that the identification of the nucleus was difficult; but the pigment granule was comparatively less in long and slender stringlike cell, in some cells it was only seen near the center, and the long elipsoid nucleus could be found. Besides, in regard to the alteration in corium, the slight perivascular round cell infiltration was found in reticular layer, but it was comparative distinctly demarcated with the circumference and this gives different feeling from the common inflammatory cell infiltration. Such nevus cell as in soft nevi was not found in any cases at all. Though there were differences in degree, in all cases chromatophore was recognized in small number in papillary and subpapillary layer.

In epidermis, the alteration was scarcely found, and the following fact was only acknowledged; the vacuolization of prickle cell, a few clear cell, or the slight spongy alteration, but there were no typical one. Though in some cases the arrangement of basal cell layer was abnormal, in general it was almost regular, the content of pigment was more or less irregular and in some part it increased even to the middle of prickle cell layer. While in some other part it was very little found in basal cell layer. The extent of increase and decrease of pigment is limited to several epidermal ridges, and thus the correlation was not admitted between the quantity and the arrangement of pigment cell in the abovementioned corium and that of epidermis.

By the way in consequence of inquiring the quantity of pigment cell, the degree of depth and the correlation between the content of pigment and the clinical color-tone in epidermis, it is considered rather natural that the blue tone is deep in those
cases in which the pigment cells were deep situated, and on the contrary the brown
tone at the inspection is found considerably in those cases in which pigment cell was
found only in the upper part of reticulum layer and pigment granule was abundant
in basal and prickle cell layer.

*Neurofibrille staining*: The existence of nerve fiber which might connect with
pigment cell was investigated in many specimens according to Bielschowsky-Seto’s
method, and I found that in few specimens nerve fiber bundles or nerve fibers ran
near the pigment cell or with course of it which intervened in the connective tissue;
long and slender stringlike fibrous pigment cells were close together and ran with
the same bend to that of nerve fiber (Plate VIII, Figure 32), but transitions of
Schwannian nuclei as in pigmented nevus were nowhere found at all. These ob-
servations resemble closely to what Ito\(^{14}\) pointed out in blue nevus. But the figure,
the middle axis of which was nerve fiber, was not found because the nerve fiber
bundles of the pigment cells of this nevus were not so remarkable as blue nevus.

Histochemical Examination. *Dopa Reaction*: According to Fujiwara’s\(^5\) ex-
periment under the title of the “Influence of formalin upon the dopa reaction”
dopa reaction becomes gradually feeble in the formalin fixation, but the fixation for
20 to 30 minutes does not influence the result at all. Thus the excised specimens
were fixed in 10% neutral formalin for 30 minutes and were cutted in frozen
section. The positive reaction was recognized in the specimen which was im-
mersed in dopa solution for two hours. This reaction is not always positive in
all pigment cells but it is positive in some of stringlike pigment cell, in which
smaller black granule than melanin granule collected especially at the margin of
the cell (Plate IV, Figure 15 and Plate VIII, Figure 33). The dendritic melano-
blast in basal cell layer was distinct and leucocyte was stained strong positive.

*Oxydase reaction*: The fixed oxydase reaction was studied by the method of
T. Ogata. This reaction which shows the blue granule in the protoplasm of myeloic
leucocyte, was negative in the pigment cell of this nevus which was full of pigment
granule, but in the stringlike cell of deep layer the positive reaction was found which
had blue granule which did not refract and was nearly as large as or slightly smaller
than melanin granule. Moreover, the petty granules were seen at or around cavity
of blood capillaries and in some cases slight positive granules were recognized at
the part near nervifiber bundle.

*Peroxydase reaction*: According to Okano C method, all nuclei were stained
blue without discrimination and in the cells of epidermis and external sheath of hair
root blue granules being accordant with chromatin were noticed. Moreover the
intracellular granules were found in the part near the basal layer. In regard to
pigment cells which were abundant in pigment granules the results were same as
the beforementioned oxydase reaction, that is, negative or difficult to distinguish.
And the intracellular granules stained in blue were seen in the stringlike cells being
short of melanin granules.

The chromatophore was sometimes remarkably positive but in many cases
negative. In the specimen which was fixed in alcohol and, embeded in celloidin
and stained by Unna’s method after cuprum sulfuricum procedure in the method
of Sato and Sekiya, minute blue granules in protoplasm were found more distinct-
ly in the cells being short of melanin granules than by Okano C method.
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**Reductive reaction by silver impregnation method:** Epidermal pigment which is indistinct in hematoxylin–eosin staining is indicated most evidently as the black granules even in rete Malpighii by Bielschowsky-Seto's method. In upper reticular layer so much reduced silver granules are found in the cells which have abundant pigment granules that each of silver granules could not be distinguished, but in lower layer these granules are found as the dark-purple black granules in string-or fiber-like pigment cells, and it is learned that intensive silver reduction is found at the oxygen area of Unna (see below).

**The investigation of oxygen- and reduction-area by Unna's permanganate-methylgreen method:** I did not recognize the particular alteration in reduction area such as horny layer, hair follicle, but in pigment cell the oxygen area which stained bluish with methylgreen was recognized (Plate IV, Figure 16).

**Hydrogen peroxide procedure:** The frozen section was immersed in 3% hydrogen peroxide aqueous solution and the pigment of basal cell layer showed remarkable fading after 24 to 48 hours, but there was no fading in the chromatophores of papillary and subpapillary layer, and the pigment cell in corium began to fade after 120–144 hours. The resistance to fading was stronger in stellate pigment cell than stringlike one.

**The influence of adrenalin:** In the specimen which was excised after local intracutaneous injection of adrenalin, pigment cells were seen distinctly because of conglomeration of each melanin granules but the cells themselves appeared somewhat constricted. I do not think that the temporary fading following local intracutaneous injection which was mentioned in the clinical observation owes only to the constriction of blood vessel.

**Meirowsky's and Bittorf's phenomena:** In the observation of the fresh specimen which was suspended over saline and incubated at 56°C according to Meirowsky⁶, already after an hour, the pigmentation of epidermis and then that of corium became remarkable after four hours, and after 24 hours the blackning finished completely and attached hairs increased the degree of blackning too. The skin specimen which was immersed in the solution of 1:1000 adrenalin at 37°C (Bittorf's method⁷) showed the mild blackning of epidermis after 24 hours.

**Fat staining:** Kreibich⁸ indicated the lipoid in the pigment cells of blue nevus. I tried Sudan III staining, but I could not recognize the positive reaction in the pigment cells.

**COMMENT**

**Review of literatures:** This disease had originally been considered as the pigmented nevus and was especially taken notice since the report of Ota and Tanino and afterwards Sakurane, Niisawa, Hanada, Nomura and Nagao reported each one case, and Hanahata and others reported 2 cases of Japanese, 5 cases of Korean, Ohara each one case of Japanese and Korean, and S. Kitamura 5 cases, Kan 2 cases of Korean, and in Manchuko and China some cases are reported.

In the European and American literatures, however, only in the ophthalmologic reports of about 10 cases could be found as the case of melanosis bulbi accompanied with cutaneous spot but the case report as the cutaneous disease is seldom found. What Goldschlag⁹ reported as the blue nevus seems to be this disease from the point of cu-
taneous spot and the pigmentation of eye-ball. In the United States the reports are made recently; in 1931 Ebert and Nomland reported the case of 23 years old female whose pigmented nevus of the sclera had became distinct 8 years before and the pigmentation of the left temple appeared 3 years before, in 1935 O'Leary, Montgomery, and Brunsting reported a case of 25 years old female as the metallic pigmentation, in 1936 Rauschkorb that of 22 years old female, it 1937 Cornell remarked the pigmentation on left face of 28 years old female, Mitchell and Scull reported the case of 47 years old Negro, in 1938 Jamieson that of 21 years old white female, Schiller and others that of 12 years old male, in 1939 Montgomery that of 17 years old female and in 1948 Rothman and others reported the case of 20 years old racial mixed female between Japanese and American. All those were casuistics at the society or discussion under the suspicion of blue nevus, Mongolian spot or argyria, and those natures were not settled, but except for the case of Schiller in all cases the borne or delayed pigmentation of the sclera was found, and it seems to be this nevus in view of the site of lesion. While in 1949 Pariser and Beermann advocated the morphological variant of blue nevus, the persistent extrasacral Mongolian spot, or the diffuse mesodermal pigmentation under the title of the wide blue-spot-like pigmentation in a case of 34 years old white male, in 1950 Cole, Hubler and Lund described minutely 4 patients as the persistent, aberrant Mongolian spot, and Meret remarked in the discussion that these pigmented nevi were called the nevus fusocacraeuleus in Japan, and these 3 out of 4 cases in accord with the case of Pariser are just undoubtendly this disease according to the description of eye-bulb, skin lesion and their histology. That is, in the United States this disease has been comparativery well observed and reported but it belongs originally to the rare disease. In conclusion, it may be said that this nevus develops without regard to race, but from its frequency it can't be denied that the Japanese who has Mongolian spot at the rate of 100 per cent is predisposed to this nevus. It may be guessed, therefore, that this is the reason before Ota's report why the brown case was considered as the pigmented nevus and the case which has the blue tone is supposed as the aberrant Mongolian spot or the variety of blue nevus.

It is a very interesting problem why the nevus is found on the region of the first or second branch of trigeminal nerve, but the explication is very difficult and can't be easily settled. That the pigmented nevus, hemangioma, etc. often develop on those parts has been generally recognized and from the figure of genetical observation which Castle incidently made in Dutch rabbit, the variations in the extent of pigmented spot by the action of modifying factor are noticed and especially the peripheral zone of eye seems to be the predisposing area of pigment spot. After all, of this pigmented spot too the following guess is only made; this pigment spot will appear on face by the abovementioned promoting factors in addition to the complex embryonic conditions.

Melanosis bulbi is the second feature of this nevus and Bourquin designated as the complete melanosis which has the three cardinal symptoms; partial pigmented spot of sclera, hyperpigmentation of iris and the dark brown colouring of fundus oculi, but some of these three may be found not only in this nevus, but in hemangioma on face especially near eyes, pigmented nevus or verrucous pigmented nevus, etc.. However, many are incomplete in Bourquin's sense in those cases
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and it is only in this nevus that complete melanosis bulbi in the sense of Bourquin is seen and this can be said one feature of this nevus.

Moreover, that in many cases erythema and wheal which appeared fast on skin in the histamine scratch test showed angioneurotic hypersensitivity of the lesion, and I think that this disturbance may have at little concern with the pigment formation of this nevus. According to the facts that the contemporal fading is observed after 5–30 minutes of local intracutaneous injection of adrenalin, that this nevus appeared or became remarkable in puberty, and that alteration of color tones was recognized in female patients in the physical changes such as menstruation or others, I guess that the pigment formation depends on the neuro-hormonal reaction.

The histological and histochemical investigation of this disease is rare, and in Japan only Tanino mentioned the histological observation of two cases; in the United States Cole and others investigated four cases, Rothman & Pinne, Mitchell & Scull, O'Leary, Montgomery & Brunsting, Ebert & Nomland made the biopsy in each one case and discussed particularly the difference with argyria and considered the pigment granule as melanin, and Cole and others, and Rothman & Pinne obtained positive dopa reaction in their cases and they stated that the pigment cell was the melanoblast and that it would be the abortive form of the aberrant persistent Mongolian spot or blue nevus.

From the results of the histological and histochemical observations which I investigated, I think that this nevus is almost similar to blue nevus or Mongolian spot; Tièche proved in the blue nevus that the pigment cells groups which pack the brown pigment granules—melanin in the cells take of various forms in connective tissue fiber at the middle layer of corium, and Sato and Stranz verified the positive dopa reaction in that pigment cell. Bloch-Bahrawy demonstrated the fact that also in Mongolian spot the oval, fusiform, stellate or dendritic pigment cells in connective tissue fiber are found and dopa reaction of these cells is positive. Ito scrutinized the abovementioned two diseases and asserted that they were the mesodermal melanoblast. Now, in the nevus fusco-caeruleus ophthalmo-maxillaris, pigment cells of various forms lay scattered in corium and the nevus cells could not be found and the pigment cells kept its color tone firmly without fading with hydrogen peroxide for 6 days. Sato and Stranz pointed out that the coexistence of the negative and positive dopa reaction in blue nevus and that there were many degrees of oxidation; my observation on this nevus was almost accordant with them and the dopa positive granules were proved in cells being scant of melanin granules, and the reaction became negative in the cell abundant in pigment granules—melanin, therefore I guess that the cell having dopa oxydase in excess perhaps becomes dopa positive in compliance with the alteration in the process of oxidation and it is surmised consequently that they were due to the same origin from the piont of the chemical nature of the pigment cell.

The remarkable oxygen-area which was revealed with methyl-green in pigment cells was recognized by Unna's method and the positive oxydase and peroxydase reactions which showed minute blue granules in the cell being short of pigment granules were noticed. These findings coincide with the following histochemical observations on pigmented nevus of Ito and Watanabe. They verified the participation of oxydase and peroxydase in melanin production and said that
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peroxydase existed in excess in nucleus moved to protoplasm, overcame the catalase action and participated in the oxidation of melanogen and that remarkable oxydase reaction was found in the state of hyperfunction of melanogenesis. From abovementioned facts the pigment cell in nevus fusco-caeruleus Ota is guessed to be a melanoblast.

In consequence of making clear from what tissue this melanoblast developed, I have observed the pigment cells, as before-mentioned, which were in contact with nerve fibre and ran with the same bend to that of nerve. But the picture of such transition or affinity between this pigment cell and Schwannian cells as was seen in soft nevus was not found at all and the absolute inseparable state was presented. And this figure is accordant with that Itô14) pointed out about the relation between pigment cell and nerve bundle in Mongolian spot and blue nevus, and consequently these cells are perhaps the cell connecting with the mesenchymal sheath of nerve (endo-perineurium). That the lesion of this nevus situated in the distribution of the 1st or 2nd branch of trigeminal nerve suggests the more the close relation with nervous system. The view that the pigment cell of this nevus is mesodermal is supported by the existence of complicated melanosis bulbi, which distributed in mesodermal tissue such as sclera, iris and choroid. Thereby I guess the pigment cell of this nevus also corresponds to mesodermal endo-or perineurium as Itô inferred about Mongolian spot and blue nevus, and blongs phylogenetically to the socalled "perineurale Pigmenthülle" of Weidenreich. Therefore, it is admitted that the histological picture, chemical nature and origin of this nevus resemble closely to those of Mongolian spot, and from the point of persistent and localized occurrence, I guess it is a kind of malformation similar to blue nevus. The differences from blue nevus are that nevus Ota predisposes the particular region which corresponds to the trigeminal nerve and complicates clinically frecklelike brown spot, histologically the increase of pigment granules in epidermal basal layer. The surrounding of orbit is the predisposing area where other pigmentation develops frequently and there exists perhaps many phylogenetic architechtonical factors such as shown in the fissurale theory of Virchow and it is supposed that this nevus belongs to the same principle. I have not enough data of explaining the pathogenesis of brown spot in this nevus but the positive Meirowsky's phenomenon suggests that epidermis is also the favorable part of oxidation.

SUMMARY

110 cases of Nevus fusco-caerules ophthalmico-maxillaris were observed during recent eleven years in our department of dermatology, and its frequency is 0.4% to the whole outpatients. The site of nevus is characteristic and it is found in the region of the 1st or 2nd branch of trigeminal nerve and in the cases of about 61.3% melanosis bulbi was recognized. The alterantion of the color tones in deepness according to menstruation, seasons, surroundings or others was recognized in 18 cases. The angioneurotic disturbance in the lesion was recognized in the histamine scratch test.

In the histological and histochemical investigation the pigment cell resembles closely to that of Mongolian spot or blue nevus as follows, the hard fading with
hydrogen-peroxide and the positive oxydase-, peroxydase- and especially dopa-reaction suggest that the pigment cell is the mesodermal melanoblast, and it corresponds phylogenetically to the mesenchymal endo- or perineurium from the observation that the pigment cell has the close relation with nervefiber. Consequently, I think the etiological mechanism of this nevus is explained in our view of pigment formation that the quantitative alternation of melanin is due to the chemical transmission controlled by the vegetative nerve.

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7) Bittorf, Arch. f. Exper. Path. u. Pharm., 1914, 75, 143.
8) Kreibich, Arch. f. Dermat., 1927, 153, 804.
11) Cole, Hubler & Lund, ibid., 1950, 61, 244.
12) Mereer, ibid. 1950, 61, 258.
14) Itô, this Supplement, 21.
15) Itô & Watanabe, this Supplement, 9.
VIII. Nevus Spilus en Nappe*

In a general way systematized nevus shows the unilateral and almost linear arrangement, and at times it involves more widespread area and especially we find rarely the lesion which consists of disseminated ephelidelike spots over the dark skin. In 1888, Jadassohn reported the “halbseitig lokalisiertes, ephelidenähnliches multiples Fleckmal” and in 1895 Jadassohn and Werner1) discussed about the correlation between this pigmentation and the distribution of cutaneous nerve in 6 cases. Gougerot, Meirowsky,2) Scholtz,3) Crocker, Ehrmann, Duhring, Sprinz, Simon, Weidemann, Robinson and others also described the analogous cases. A female with the diagnosis of lentiginose profuse systematisée héréditaire by Aguilera and Cifrian4) seems to be this disease. In Japan 3 cases of Matsumoto5), Ninomiya,6) one case each of Tanioku7) and K. Kitamura8) are reported.

Symptoms: According to the descriptions of the predecessors and our observations (see below), this affection is found frequently in a slight dark complexioned persons rather than a blue-eyed White. The whole lesion is light brown or grayish black in color as Recklinghausen's freckles or pigmented spots. The border is indistinct or zig-zag. There are oval or polygonal irregular ephelidelike spots of millet seed to half rice grainsized over the lesion. The color of these spots varies from light brown like ephelides to blackish brown like pigmented spots and they do not elevate over the cutaneous surface. The density and arrangement of these spots are not constant and in exaggeration they give one the impression of the sesames which are scattered over a dirty table cloth. Furthermore some cases which show the slight hypertrichosis over the blackish brown skin seem to be a type of this affection.

Site of lesion: In general it takes place unilateral and spreads broad zoniform or napkin like in shapes over the neck, nape, shoulder, chest, back, upper arm (rarely on the forearm) and abdomen, and thus it seems suitable to call this as naïvi spili zoniformes or naïvi en nappes. The correlation between this nevus and the distribution of cutaneous nerve is as follows; the area of from C3 to T4—T7 is involved most frequently, but in some cases the area of from T10—T12 is affected. Therefore, there is close connection between this nevus and the cutaneous nerve. Thus this spot should be treated and classified as a kind of systematized nevi which are called nerve nevi.

Report of cases: Table VIII showed the patients of this nevus in recent 10 years in our clinic. No sexual difference was found. In most cases the disorder was found after birth but the nevi with slight color tone were noticed in puberty. Left side was oftener than right side and the cases with the pigmentation over the shoulder region were found most frequently. Two cases in Table VIII (16th and 17th case) were observed by Miura at the dermatological clinic of Nihon University and he offered us the specimens for biopsy.

* By Minor Itó and Yoshiro Hamada.
### Table VIII

<table>
<thead>
<tr>
<th>Case number</th>
<th>Age in years</th>
<th>Sex</th>
<th>Age of onset</th>
<th>Location</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24</td>
<td>F</td>
<td></td>
<td>Left loin</td>
<td>Concomitant Bourneville-Pringle’s disease</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>F</td>
<td>Inborn</td>
<td>Left neck, chest and back</td>
<td>No color-changes in menstruation</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>M</td>
<td>Inborn</td>
<td>Left chest, back and upper arm</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>21</td>
<td>M</td>
<td>Inborn</td>
<td>Left shoulder, axilla and upper arm</td>
<td>Concomitant chloasma gravidarum</td>
</tr>
<tr>
<td>5</td>
<td>32</td>
<td>F</td>
<td></td>
<td>Left shoulder and upper arm</td>
<td>Antipyrene fixed eruption over the center of the nevus</td>
</tr>
<tr>
<td>6</td>
<td>28</td>
<td>F</td>
<td>Inborn</td>
<td>Left shoulder and upper arm</td>
<td>Quite same distribution to herpes zoster on the right side of the back</td>
</tr>
<tr>
<td>7</td>
<td>48</td>
<td>F</td>
<td>Inborn</td>
<td>Left back</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>22</td>
<td>F</td>
<td>Inborn</td>
<td>Left neck, shoulder, chest and upper arm</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>51</td>
<td>F</td>
<td>Inborn</td>
<td>Right chest, back, thigh and abdomen</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>21</td>
<td>F</td>
<td>Inborn</td>
<td>Right neck</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>26</td>
<td>M</td>
<td>Inborn</td>
<td>Right chest (on the niveau of both nipples)</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>18</td>
<td>M</td>
<td>About 13 years</td>
<td>Left shoulder and back</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>26</td>
<td>F</td>
<td></td>
<td>Right abdomen and flexor-surface of thigh</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>20</td>
<td>M</td>
<td>Inborn</td>
<td>Left cheek and neck</td>
<td>His father has pigmented moles and his mother has ephelides</td>
</tr>
<tr>
<td>15</td>
<td>20</td>
<td>M</td>
<td>About 7 years</td>
<td>Left chest, shoulder and thigh</td>
<td>Hypertrichosis of the central part of the nevus</td>
</tr>
<tr>
<td>16</td>
<td>21</td>
<td>M</td>
<td>About 18 years</td>
<td>Right shoulder and extensor-surface of upper arm</td>
<td>Hypertrichosis of the central part of the nevus; consanguineous marriage among parents of patient</td>
</tr>
<tr>
<td>17</td>
<td>23</td>
<td>M</td>
<td>About 19 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>17</td>
<td>F</td>
<td>Inborn</td>
<td>Left shoulder and extensor-surface of upper arm (see Plate X, Figure 41)</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>22</td>
<td>M</td>
<td>About 17 years</td>
<td>Left shoulder, axilla and flexor-surface of upper arm</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>22</td>
<td>M</td>
<td>Inborn</td>
<td>Radial surface of the back of left hand</td>
<td>Hypertrichosis of the central part of the nevus</td>
</tr>
<tr>
<td>21</td>
<td>31</td>
<td>M</td>
<td>Inborn</td>
<td>Left chest, right forearm</td>
<td>Several depigmentations on ileogluteal region</td>
</tr>
</tbody>
</table>
Clinico-biological Investigations: a) Sensory and Diaphoretic Tests—Disturbances of sensations were found in 5 cases out of 21 cases and diaphoretic disturbances were found in 2 cases out of 4 tested cases (Table IX).

### Table IX

<table>
<thead>
<tr>
<th>Case number</th>
<th>Local disturbances of sensation</th>
<th>Local disturbances of diaphoresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>Hypoesthesia, hypalgnesia and thermohypoesthesia</td>
<td>No difference of diaphoresis between normal skin and the nevus</td>
</tr>
<tr>
<td>17</td>
<td>Hypoesthesia, hypalgnesia and reduced feeling of cold but normal of heat</td>
<td>Pilocarpine method showed slight sooner diaphoresis in nevus rather than in normal skin</td>
</tr>
<tr>
<td>18</td>
<td>Thermohypoesthesia, normal sensation of touch and pain</td>
<td>No diaphoresis in 14 minutes after pilocarpine method in the central part of the nevus</td>
</tr>
<tr>
<td>19</td>
<td>Thermohypoesthesia in the central part of the nevus</td>
<td>Adrenalin method (Wada) showed no distinct difference of diaphoresis between normal skin and the nevus</td>
</tr>
<tr>
<td>20</td>
<td>Hypalgnesia in the central part of the nevus and normal feeling of temperature</td>
<td></td>
</tr>
</tbody>
</table>

b) Histamine Scratch Test

### Table X

<table>
<thead>
<tr>
<th>Case number</th>
<th>The differences in the development of wheal between normal skin and nevus</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Simultaneously (100 seconds)</td>
</tr>
<tr>
<td>8</td>
<td>Simultaneously (80 seconds) then erythema diffused over the nevus</td>
</tr>
<tr>
<td>9</td>
<td>Simultaneously (80 seconds)</td>
</tr>
<tr>
<td>15</td>
<td>Simultaneously (165 seconds) but wheal over the nevus was faint</td>
</tr>
<tr>
<td>18</td>
<td>Simultaneously (90 seconds)</td>
</tr>
<tr>
<td>19</td>
<td>Wheal developed over the nevus later and disappeared sooner than the normal skin</td>
</tr>
<tr>
<td>20</td>
<td>Wheal developed at the 9th minute over the nevus and existed for 12½ minutes</td>
</tr>
<tr>
<td>21</td>
<td>Wheal developed at the 130th second over the nevus and existed for 30 minutes</td>
</tr>
</tbody>
</table>

The fact that in the 6th case a coin-sized antipyrine fixed eruption was found on regio acromialis which corresponds to the center of the nevus was also the suggestion of the disturbance in angioneurotic nerve.

**Heredity:** Siemens described the frequent family occurrence of nevi pigmentosi spili, he noticed the concordance in 21 cases out of 56 twins. We noticed the pigmented spot and ephelides in parents of patient in the 14th case and the consanguineous marriage among parents of patient in 17th case but could not observe the certain evidence of inheritance at all.

**Histological studies:** Four cases (16th, 17th, 19th and 20th case) were studied. The principal alteration was the increase of melanin granules in basal layer, esp.
abundant at the top of epidermal ridges and sweat-pores. Furthermore they diffused in two or three layers of prickle cell layer. Epidermal ridges became slender, basal cells were prismatic and arranged like a palisade. At times the perinuclear vacuolization of Malpighian rete cells was found. No alterations were found in granular and horny layer. Papillae were projected distinctly equivalent to the epidermal ridges, and dilated blood capillaries were filled with blood cells. The blood vessels of subpapillary and rete layer dilated also and the slight perivascular round-cell infiltration was noticed. Chromatophore was relatively increased in number in papillary and rete layer. But nevus cell could not be found anywhere. The sweat-duct and sweat-gland slightly dilated but sebaceous gland was normal. The significant changes in connective tissue or elastic fiber could not be found approximately.

**Diagnosis:** Jadassohn concluded that these nevi are the frecklelike and Ehrmann considered them chloasma-like pigmentation. In the schema which was established by Pollio\(^{10}\) these nevi are classified into the pigmented nevus-like Recklinghausen's disease. But this disease has a somewhat indistinct bordering and unilateral arrangement. Furthermore, histologically, these nevi have no nevus cells and they are easily distinguished from soft nevi. Thus we consider them as a type of systematized nevi and the signature nevus spilus en nappe may be the most suitable one for their clinical manifestations.

**COMMENT**

Concerning the pathogenesis of systematized nevi the participation of nervous system has been studied by many investigators, although we have not come to a definite conclusion as yet. Since the neurogen concept of Bärensprung\(^{11}\) (1863) Grosser, van Rynberk, Haecker and others studied the pigmented flecks of animals. In French school Philipson,\(^{12}\) Hallopeau,\(^{13}\) Gougerot and Noce, Klippel and Weil\(^{14}\) mentioned the neurogen theories and metameric theory of Alexander and Blaschko,\(^{15}\) phylogenetical observation of Meirowsky or Jadassohn were reported. These are suggestive of concerning of cutaneous nerve with the pathogenesis of nevus, but several investigators maintain that the nevus does not always coincides with the distribution of cutaneous nerve in arrangement. But it seems difficult to arrive at a single conclusion because of reasons such as complexed peripheral innervation of skin, interference of vegetative and sensible nerves, individual variations and the difficulties in the histological and physiological investigation of cutaneous nerves. Therefore following cases are mentioned as the clinical and complemental evidence of this subject; nevus-like pigmentation caused by bullet (Falkenstein),\(^{16}\) linear nevus after breast injury (Nontkowski), pigmented nevus after neuritis (Meirowsky), linear nevus accompany with the anomaly of cervical-rib of same side (Lévi and Tzanack\(^{17}\)), systematized nevus accompany with sclerodermod and pain (Queyrat, Lévi and Rabut\(^{18}\)), nevuslike pigmentation with circumscribed disturbance of sympathetic nerve (Laignel-Lavastine), etc. and especially a female observed by Lewith\(^{19}\) is interest. The patient presented those homolateral sensible and trophoneurotic disturbances such as thermohypesthesia which coincident to the flat pigmented nevus over right half of chest and upper extremity (C\(_4\)—D\(_7\)) and increased sweating of right axilla, asymmetry of face, anisocoria, hypoplasry of right mamma,
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hypertrophy of left deltoideus and left handedness. And Lewith pointed out the conception of Kyrle which mentioned that the sympathicus regulates the pigment formation and emphasized the close correlation between pigmented nevus and homolateral nervous disturbance. Recently Horiuchi\(^2\) reported a case of pigmented nevus accompanied with localized hyperidrosis and we remember the several cases reported by Eppinger which have unilateral pigmented nevus and malformed kidney of the same side.

We noticed in this article the homolateral nervous disturbances (reduced sensibilities, sweating anomaly and the notable differences of histamine wheal between nevus and normal skin) in the abovementioned nevi spili en nappes and especially in our 7th patient the nevus showed quite same arrangement and distribution but in opposite side to that of herpes zoster. This observation corresponds to that of Bärensprung and Simon\(^2\) in which systematized nevus arranged coincidently to the distribution of herpes zoster and they surmised the alteration in ganglion.

Moreover in the histological investigation of pigmented nevus, Mongolian spot, blue nevus and nevus fusco-caeruleus we have obtained the data which indicate the relation to the neurofibril, thus we think much of the participation of nervous factor in the pathogenesis of systematized pigmented nevus.

**Summary**

The cases of nevus spilus en nappe which is a type of systematized nevus were reported and the homolateral nervous disturbances were noticed. Thus we believe that these observations are the best materials to suspect the concept of participation of nervous element in the pigment formation.

**References**

1) Werner and Jadassohn, Arch. f. Dermat., 1895, 33, 341.
2) Meirowsky, Arch. f. Dermat., 1921, 134, 1.; Jadassohn's Handb. IV/2, 1933, 652.
3) Scholtz, Jadassohn's Handb. XII/2, 1932, 567.
4) Aguilera and Cifrian, Actas Dermo-Sifiliol, 1944, No. 9.
5) Matsumoto, Dermatogy I, Kioto 1928.
9) Siemens, Jadassohn's Handb. III, 1929, 139.
10) Pollio, Arch. f. Dermat., 1906, 80, 47.
14) Klippel and Weil, Presse Méd., 1922, 30, 388.
15) Blaschko, Dermat. Zeitschr., 1895, 2, 361.
18) Queyrat, Lévi and Rabut, ibid., 1921, 28, 116.
IX. Nevus Depigmentosus en Nappe

In the Negro, Meirowsky\textsuperscript{1)} reported the cases which resemble the nevus systematicus depigmentosus but such cases are rare in Japan. Moreover vitiligo presents occasionally systematized arrangement and thus the diagnosis is to be established after careful examinations.

This study is based on the observations of several cases of nevus systematicus depigmentosus which are arranged similar to the nevus spilus which was studied in the preceding report.

\textit{Case 1.}—Male, aged 27, seen at our clinic on Oct., 1950 suffering from the depigmentation over the shoulder region which becomes apparent a half year after birth. His maternal grandfather had pigmented moles. Examinations: The moderate stature and well nourished. A pale depigmented lesion (CIV–CVI) over the right scapular region to the regio deltoidea and faint brown frecklelike spots in size of millet-seed were scattered over this area (Plate X, Figure 42). The bordering of the area was zig-zag and the depigmentation was light in color in the area from the median margine of right scapula to the median line and thus the bordering to the normal skin was not so distinct. Furthermore several blackish brown lentigolike spots were indicated over this area. No erythema or squama was noticed and no paresthesia or hypesthesia was observed. The histamine scratch test showed no differences between the normal and the depigmented skin. The pilocarpine test (Minor-Wada’s method) showed the fast diaphoresis by 30–60 seconds in the depigmented area but the difference in degree of diaphoresis was not found. Aschner’s phenomenon negative, basal metabolic rate +5\%. Increased urobilinogen in urine.

Diagnosis: The disorder is inborn and distinguished from vitiligo because of the absence of hyperpigmented areola. In lepra the presence of disturbances in sensations and thickened nerve readily establishes the diagnosis. From Recklinghausen’s disease this can be distinguished by the zig-zag bordering as the significant feature of systematized nevi which was mentioned by Siemens and there was of course no neurofibroma. Thus we think the nevus systematicus depigmentosus en nappe should be brought into the diagnosis of this depigmentation.

\textit{Case 2.}—Female, aged 26, consulted our clinic at first on July, 1950. Examinations: Physical examination negative. She presented the nevus fusco-caeruleus ophthalmomaxillaris Ota over the right temple and cheek and the irregular palmsized depigmented lesions over the radial side on the flexor surface of right forearm. The pigmented spots brown in color, varied in size from that of half rice-grain to a lentil were scattered over this area. Moreover several irregular coinsized depigmentations were jointed with each other over the flexor surface of the right upper arm to the distribution of n. cutaneous brachii medialis. Further each one depigmented spot of palm in size were found over the right mamillary region (TIII–TIV) and the flank

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(TIX—TX). These depigmentations were light and not so distinct in color as much as vitiligo and no erythema or squama was found over these spots. The histamine scratch test was performed at the most distinct spot over the forearm and the wheal developed after 1½ minutes on both normal and depigmented skin. The local injection of hypophysis hormone and hematoporphyrin did not develop the pigment.

Case 3.—Female, aged 20 seen at first on Aug., 1947. She stated that since 3 years she had had the several dotted leucodermae over the left thigh and that they increased in number recently. Examinations: Blood count normal, urinalysis negative, regular menstruation, basal metabolic rate +14%, Aschner's phenomenon negative. Ephelides on the face. Many dotted depigmentations varied in size from that of a millet seed to a half rice-grain, follicular or not, arranged in groups, were found over the area from median side of knee downwards obliquely to the front surface of left leg. The bordering was distinct but no hyperpigmented areola, erythema or squama was seen over the depigmentation. The entire lesion corresponded to the distribution of rami cutanei cruris medialis (L4v). The histamine scratch test showed the wheal development at 1½ minutes over the normal skin but no wheal was noticed after 3 minutes in the depigmented area. Histologically, the depigmented skin showed decreased melanin granules in basal layer of epidermis than normal skin and in some part they were disappeared entirely. Moreover in this part the basal cells were shortened and swollen and their nuclei were ovoid in shape and the perinuclear vacuolization, furthermore melanoblaste épuisé (Masson) was noticed. Thus these basal cells were distinguished from the normal palisadelike arranged cylindrical basal cells because of their disarrangement. This finding was most evidently observed in the silver impregnation, that is to say, the basal cell layer seemed like a clear unstainable zone. The blood capillaries under the depigmented area dilated moderately and the perivascular zone seemed to be spongious but there was no cell infiltration. The other parts in epidermis and corium were normal. The elastic fiber and Gitterfaser showed no alteration. The local injection of hematoporphyrin and Vitamin B2 in the depigmented area was not efficient.

Case 4.—Female, aged 16, was first seen in our clinic on Aug., 1941. The patient noticed the verrucous eruptions over the neck since 1 year of age. Examinations: Physical examination negative. Urinalysis negative. A nevus systematicus acneiformis over the left foreneck in the oblique direction. Furthermore a depigmented spot in size of a coin was situated under lateral of it. The entire lesion corresponded to the distribution of CIII. The histamine scratch test over the nevus acneiformis indicated the somewhat delayed development of wheal and no wheal was found over the depigmented area.

Summary

4 cases of nevus systematicus depigmentosus were reported. In these cases there were no atrophy which was mentioned by Leven in nevus linearis atrophicus depigmentosus and thus we think that they were surmised as a simple depigmented nevus. But the facts that the nevus takes place over the definite distribution of cutaneous nerve and that they indicated some significant differences against normal skin in the histamine scratch test are suggestive of the homolateral disturbances of nervous system. We consider them as the favorable data for our theory of melanin.
production.

References

1) Meirowsky, Arch. f. Dermat., 1921, 134, 1; Jadassohn’s Handb. IV/2, 1933, 652.
2) Leven, Arch. f. Dermat., 1922. 140, 403.
X. Incontinentia Pigmenti (Bloch-Sulzberger)*

In 1925 Bloch reported a young female case of "hitherto undescribed congenital pigmentary disturbance" under the title of "incontinentia pigmenti." Sulzberger made in Bloch's clinic an extensive report on this subject in 1928. Subsequently, Naegeli demonstrated an analogous case with family occurrence and named this chromatophore nevus. Siemens in 1929 presented a case under the name of melanosis corii degenerativa. His case was admitted by Sulzberger as belonging to this disease. Later Bardach noticed similar cases in twins. The identity of his cases with former cases was eagerly discussed by Siemens and Meirowsky-Leven and thus attracted the attention of all investigators in the world. The number of this rare condition reported in the literature amounted to about 40. The first case in Japan was observed by K. Kitamura and at the 250th meeting of the Tokyo Dermatologic Society Yokoyama demonstrated the second case, and the present author observed 3 cases. These are illustrated in Table XI.

| Table XI |
|-----------------|-----------------|-----------------|
| Patient No. | 1 | 2 | 3 |
| Sex | F | F | F |
| Age | 11 months | 7 months | 26 years |
| Consanguinity and family occurrence | None | None | None |
| Onset | 10 days after birth | Existed by birth | 100 days after birth |
| Initial eruption | Erythematous eruption with intermittent fever | Erythematous exanthema | Varicelliform eruption |
| Symptom | Mortar splash-like pigmentation dark brown in color with undulated zonal arrangement. Zebra-like appearance | Bluish-brown splash-like pigment patches with marble configuration | Slaty ash brown pigmentation stellate in form |
| Location | Symmetrically generalized | Symmetrically generalized | Systematized on the breast, shoulder and flexor surfaces of extremities |
| Other symptoms | Stupid appearance. Slight microcephalia and sudden death by pneumonia | Congenital nuclear cataracta of the left eye | Asymmetry of the mamma |

Clinical Appearance: In typical cases stellate mortar-splash-like pigment patches varying from slaty ash brown to bluish lead-hued in color, are observed in reticulated arrangement. In cases reported by Siemens, Kitamura, Schuermann and Yokoyama, systematized arrangement is ascertainable. In my first case I de-

* By Minor Itô. Published in this Journal, 1951, 54, 67.
Incontinentia Pigmenti

scribed exaggeratedly as zebra-like appearance. So it is natural that the differentiation from systematized nevus was eagerly discussed in Bardach’s case. The surface of the lesion is usually flat but sometimes is somewhat elevated or slightly atrophic and dent. Occasionally desquamation may be present. At lower abdomen and ends of extremities the lesion may take verrucous appearance. In most of the cases the eruption is more or less generalized, but the severity may differ on the left and right side.

Inflammatory Changes at the Onset: It was already noticed since Bloch and Sulzberger that such inflammatory changes as erythema, swelling, lichenoid eruption or zosteriform vesiculations may be accompanied at the onset. This is observed in almost all cases except for the cases of Naegeli, Moncorps, Nexmand. However, no investigators attached great importance to this fact, till Heilesen emphasized its significance. Uebel et al. paid attention to the fact that in his case the mother had suffered from febril disease in the 6th month of pregnancy. He surmised that there exists some causal relationship just as the incidence of malformations through infection or intoxication of the mother in the fetal period. Thus he emphasized the rôle of maternal influence during pregnancy and called this embryopathia via adrenalsystem. Similar case was reported also by Haber.

Clinical Course: The clinical course is somewhat characteristic, i.e. the primary onset is noticed soon after birth and the lesion which becomes gradually intense till in 4 or 5 years of age begins to subside untill complete recovery. This peculiarity in the clinical course as well as the inflammation at the onset is regarded as important differentiating point from systematized nevi. Sulzberger’s case and my third case in which the eruption persisted till 19 and 26 years of age respectively are exceptional ones in this point.

Complications: From the report of Bloch-Sulzberger the complications of various congenital malformations espec. abnormalities in the psychic, nervous and optical systems were described by many authors. Most often debility, nervous irritability, microcephaly, retrobulbar glioma, strabism, nystagmus, spasm of extremities and heart failure are reported. Especially in Sulzberger-Fraser-Hutner’s case congenital anopsy and ectodermal dysplasy are associated, and in Heilesen’s hare-lip and convergent strabism are noticed in the family. On account of this frequent combination with various malformations in ocular system, Uebel, Ludwig and Korting proposed a hypothesis concerning to its etiology in reference to dysgenesis mesodermalis corneae et iridis of Rieger or retrolental fibroplasia of Terry. In my second case congenital nuclear cataracta was associated.

Heredity: In the case of Naegeli father and two of daughters were affected. Sulzberger’s case originated from a family with female-linked congenital ectodermal dysplasia. Further Sobel observed a case of a young Chinese girl who’s father presented suspicious eruption for incontinentia pigmenti. In Japan Kitamura reported two cases with family occurrence. Anyway the onset in infancy and the frequent combination with congenital anomalies suggest that incontinentia pigmenti has at least partial relationship with congenital factors. Nearly all of the cases reported in the literature are female cases except for Moncorps’s case. This, too, is interesting in the genetical survey of this disease.

Histopathology: The characteristic histological change is the increase of pigment
Studies on Melanin cells in the upper dermal layer. They are stellate or fusiform and are located mostly near blood vessels and contain large amount of coarse melanin granules (Plate X, Figure 39). Their dopa reaction is negative and they are held to be endothelial or connective tissue cell by Bloch-Sulzberger, though recently Carol and Bour obtained positive dopa reaction in these cells. In the basal layer in the pigmented area, the melanin content is rather decreased and existing melanin granules are smaller and various degenerative changes such as vacuolization in the protoplasm and pycnotic nuclei are noticed in the basal cells (Plate X, Figure 40).

The inflammatory changes in the pigmented area consist of cellular infiltration of connective tissue cells and lymphocytes, plasma cells and edema of papillary layer and dilation of blood vessels. And eosinophilic cells are observed by Kitamura, Carney and Yokoyama. The former two described also intraepidermal vesiculation containing eosinophilic cells. Uebel et al. called attention to the swelling of endothel cells of arterioles in the cutis, and suggested some relationship with allergic-hyperergic inflammation like periarteritis nodosa. In my histological study of the third case no inflammatory changes are noticed as in Sulzberger’s case. It is, however, quite natural that inflammation should have subsided after such a long interval.

Doornink studied histologically on pigmentation in Riehl’s melanosis, poikiloderma, lichen ruber and drug eruption and obtained similar results as in incontinentia pigmenti. Thus he came to the conclusion that the term incontinentia pigmenti is not the name of special disease but a histo-pathological symptom.

COMMENT

On the ground of the histological study and the dopa theory, Bloch and Sulzberger explained the pathogenesis of this disease in the following manner. In the normal epidermis the melanin which is produced in the basal layer is mostly transported to the upper layer. In this condition the epidermis has become incontinent of the pigment and the melanin granules drop down to the corium and are phagocyted by chromatophores. This theory was also supported by the experiment of Miescher who by injection of dopa melanin in the vitiliginous area observed that artificial melanin is sustained for a long time in the chromatophore. Siemens accepted Bloch’s theory, but at the same time assumed that the melanin in basal layer is increased in view of the darker skin color. In my material I obtained analogous results to Bloth-Sulzberger’s. The existence of argentaffin granules in the basal layer as well as the negative dopa reaction is in favor of his theory. Further the frequent observations of compensatory increased dermal pigmentation in cases of scanty pigment content in the epidermis in animal kingdom may support this view. However, owing to the rarity of this disease there remain many questions which are to be solved. Especially the significance of the inflammation at the onset is not thoroughly understood. It is true that inflammation may activate pigment production as in the cases of tar spread, arsenical intake or actinodermatitis. However, it is impossible to attribute such generalized occurrence of inflammation vaguely to congenital factors only. In the following the author tries to investigate this problem chiefly in connection with the study of the nervous system.

1. The peculiar systematized arrangement of this disease was already admitted in the discussions of Bardach’s case. The participation of cutaneous nerve is natural-
Incontinentia Pigmenti

1. Incontinentia Pigmenti is often suspected as in systemicized nevi. So the Voigt's border line of the termination of nerve or Blaschko's dermatom arrangement line is proposed to be the site of predilection. The location in typical cases is in arciform from the breast region to the shoulder and descends along the upper arm, quite corresponding to the Voigt's line.

2. In usual dermatoses the eruption is convex-bordered in accordance with a vasomotor nerve, while in this disease the morphology of the larger eruption is characteristically concave contoured. How is this concave form explained? Here I tried to find some special significance. First of all the reagibility of the vasomotor nerve was examined by histamine scratch test. In the pigmented area the development of the wheal was earlier than the surrounding normal zone by 10–15 seconds. This fact suggests that there exists congenital abnormality either morphological or functional in the distribution of the vasomotor nerve especially in the constrictor portion. This interstice in the distribution of the vasomotor nerve is the site of predilection and thus the typical concave form is explained.

3. From above mentioned hypothesis the occurrence of inflammatory changes at the onset is explained in the following manner. In individuals possessed of congenital labil autonomic nervous system there may arise abnormal reactions to external stimuli of the extrauterine environment. These reactions give rise to inflammatory changes especially in the interstice of the vasoconstrictor portion and thus result in the disturbance of pigment metabolism. The abovementioned acceleration of the histamine test may have disclosed the remainder of this local disposition. And, further, eosinophilia noticed by Kitamura may be interpreted as a manifestation of abnormality of tonus of autonomic nervous system. The maternal influence in fetal period and the histological resemblance with allergic inflammation of the arterioles mentioned by Uebel and others wait for further confirmation and will not be touched here.

4. The pigmentation in this dermatose usually disappears by 4–5 years of age like Mongolian spot. This is explained either as the common characteristics of dermal pigment cells or as the results of compensation through the regulatory function of peripheral autonomic nervous system in the loco or through chemical transmission. This is quite corresponding to the observation of Lassar and others that systematized nevi may disappear by itself . . . the characteristics of so-called nerve nevus.

In my third case as well as in Sulzberger-Fraser-Hutner's the pigmentation persisted till the youth like the persistence of Mongolian spot in form of blue nevus.

5. In all reported cases the pigmentation is most prominent in the perimammary region, and there the eruption persists longer than in other area. In the case of Sulzberger-Fraser-Hutner the breast of the diseased side was smaller than the other. In my third case the left mamma where the pigmentation was much darker, was by far smaller than the right (Plate IX, Figure 36). I assume that this indicates the retarded development of this merocrine glands in the sense of homolateral nervous disturbance, i.e. congenital asymmetrical distribution of trophic nerve. In accordance with this theory I observed two female cases of systematized nevi in the breast region with smaller mamma of diseased side. In another case of a 20 years old girl with hairy nevus on the breast asymmetry of the mamma was noticed. These facts as well as Lewith's(11) similar observation are in favor of my foregoing assumption,
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The relationship between melanin production and nervous factor has been established by the experiments of Brücke, Pouchet and v. Frisch on the chameleon and turbot. On the ground of these investigations Parker in 1932 proposed the theory of neurohumoralism. In human being many observations suggest that there exists correlation between nervous system and melanin production. The recent observation of Miura\(^{17}\) of the pigment borderline on Bolk-Sherrington-Foerster’s axillary line is the full suggestion of this point. The present author has already reported many observations regarding this problem.

Summary

This disease occurs in individuals with congenital dysfunction on the part of autonomic nervous system. These easily react with various grades of inflammatory changes against external stimuli of the extrauterine environment. The inflammation results in the disturbance of melanin metabolism and further in the incontinence of the epidermis. Thus the pigmentation is produced in the characteristic symmetrical and concave arrangement. But the recovery can appear sooner or later when the interstice is compensated by the interaction of peripheral nervous system.

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XI. Incontinentia Pigmenti Achromians

A Singular Case of Nevus Depigmentosus Systematicus Bilateralis*

Case

A 22 years old Japanese girl. Date of the first consultation Oct., 1950. Her father died of stomach ulcer. No dermatological disorders in the members of the family. She had had often exanthemas on various parts of the body and suffered from chilblain for the past few years. Already in the childhood, a leucodermatous patch appeared on the breast which grew more marking gradually and since two years extended to the upper arms on both sides.


Cutaneous changes: The entire skin surface was somewhat dry, and slight follicular hyperkeratosis was noticed on the elbow, shoulder and nates. On the trunk and extremities symmetrical leucoderma with systematized arrangement was noticed. On closer observation, most prominent was the one on the upper half of the body. Beginning from the breast and till the flexor surface of the upper arm, the skin looked as if the normal pigment was brushed off. Upper and outside of the breast region on both sides, there were many irregular shaped, zigzag bordered mortar splash-like depigmented spots (Plate IX, Figure 38). Several lines of islets of leucoderma ran laterally beginning from these spots. They ran along the axilla and medial of upper arms down to the middle of forearms on the ulnar side where they vanished gradually. Other lines of islets were arranged on both sides of the breast to the back sporadically. Similar zoster-like arrangement was observed more clearly on the abdomen, and, to some extent, at inguinal, gluteal and femoral regions. In short, all patches of depigmentation were arranged in accordance with Voigt's demarcation line of cutaneous nerves.

Depigmentation was most remarkable on the breast and upper arms, where it could be easily distinguished in this case who had ordinary complexion of our race. But on the lower half of the body, the depigmentation was rather obscure and might be overlooked at the first glance. The morphology of each spot was concave bordered without halo of hyperpigmentation in contrast to vitiligo. Inflammatory changes such as erythema and desquamation were completely lacking. On the breast where the depigmentation was most prominent, some of the spots showed slight depression in appearance resembling atrophy. In general, leucodermatous area was somewhat wider on the left side of the body than on the right, and, in addition, the mamma of the left side was smaller than the right.

Biological experiments: 1. Histamine scratch test was made at the leucodermatous

* By Minor Ito.
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area including surrounding normal skin with 0.1% solution of histamine hydrochloride. Erythema was noticed after 20 seconds. After 2 minutes and 15 seconds, wheal formation in the former part by 15 seconds later than in normal area, but after 3 minutes and 40 seconds both wheal showed same intensity. The disappearance of the wheal occurred in 50 minutes at the diseased site and in 90 minutes in the normal. Dermographism was negative at each site. 2. Diaphoresis was examined by Wada's modification of Minor's method. Diluted tincture of iodine was applied to the skin and after drying emulsion of starch in castor oil was spread. Then 0.6 cc. of pilocarpine hydrochloride was injected hypodermally. In leucodermatous patches no change was noticed after 30 minutes, while in the surrounding area innumerable black dots appeared in 10 minutes. 3. Capillary resistance was examined by the suction method similar to that of Hecht. The control datum was 13 cm Hg. at infraclavicular region. By 18 cm Hg. 10 bleeding dots were observed in the depigmented area in contrast to 1 in the neighbouring zone.

Histopathology: Histological specimen was excised from the left upper arm. In the epidermis no changes were noticed in the horny, granular layer and in the rete. In the basal layer, melanin granules, which were evidently identified in the normal part, were completely lacking. Even with silver impregnation method no black granules were noticed in the leucodermatous area. And there some basal cells were slightly disordered, with their swollen nuclei and protoplasm and with perinuclear vacuole formation. However, the total thickness of the epidermis and the form of epidermal processes were normal. Chromatophores in the surrounding zone was located mostly perivascular and apart from these free melanin granules were scattered here and there. In the diseased part neither chromatophores nor free granules of melanin were found, and the capillaries in the papillary layer were slightly dilated with their swollen endothels and connective tissue fibers apparently scarce. By soaking the slice in hydrogen peroxide solution for 24 hours the melanin in the basal layer faded out completely while that in chromatophores turned to pale yellow. No morphological changes were seen in nerve fibers with Masson's staining.

Diagnosis: It is easy to differentiate this from leucopathia reticularis et punctata symmetrica Matsumoto1 and from vitiligo on account of the clinical picture. It is proper to enlist this in the group of nevus, nevus depigmentosus systematicus bilateralis. In this case, however, the arrangement of depigmented spots conforms in toto with that of the third case in my former report on incontinentia pigmenti2 —only in this case the pigmentation was displaced by depigmentation, the negative picture of incontinentia pigmenti. So it is easy to remind one of the clinical picture of this case by naming this incontinentia pigmenti achromians, though there is some curiosity of this denomination.

Comment

In my former report I tried to explain the pathogenesis of incontinentia pigmenti in the following manner. In individuals with unstable vegetative nervous system, there may arise abnormal inflammatory reactions to external stimuli of the extraterine environment through the dysharmony of vasomotor nerve. These are followed by the disturbance of melanin metabolism and consequently gives rise to concave
Incontinentia Pigmenti Achromians

contoured pigmentation on the Voigt's line. But sooner or later spontaneous recovery is procurable by the compensation through the peripheral nervous system.

The case presented here is quite persuasive of this assumption. The dysfunction of vasomotor nerve is disclosed by the results of histamine scratch test, retarded perspiration and by reduced capillary resistance. And the concave contour and the unique arrangement suggest us that Voigt's line is the site of predilection and further that this disease had occurred on the congenital abnormality in the distribution of the termination of vegetative nervous system in Voigt's borderline. My observation, in common with the results of animal experiments of Brücke, Pouchet and v. Frisch (hyperpigmentation after sympathectomy) and the idea of pigment borderline of Miura, is in favor of my advocation—the participation of vegetative nervous system in pigment production.

The asymmetry of the breast glands in this case as well as in Sulzberger-Fraser-Hutner's and my third case of incontinentia pigmenti and the three cases of pigmented hairy nevus in my previous report, is assumed to be indicative of the retarded development of the merocrine gland through the congenital asymmetry of trophic nerves in the sense of homolateral nervous disturbance of Kyrle or Lewith.

SUMMARY

A case of systematized depigmented nevus is reported, which shows, as it were, the negative picture of incontinentia pigmenti. Such incidence is in favor of my theory, the participation of the vegetative nervous system in pigment production.

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XI. Malignant Melanoma

Research on the melanoma was initiated by Laennec (1806). Müller considered it to be a kind of carcinoma. But Virchow pointed out the existence of melanosarcoma and asserted that there was the mixed form of melanosarcoma and melanocarcinoma, namely melanocarcinomasarcoma. Since then, this problem has been discussed by many authors. Ribbert asserted that melanoma was chromatophoroma and Lubarsch declared that it was melanoblastoma. Miescher described that it was proper to adopt clinically the term melanomalignoma. Thus the pathogenesis of melanoma had been discussed in association with the problem of the genesis of nevus cell in pigmented nevus, Mongolian spot cell and blue nevus cell, but there are still many differences of opinion. In U.S.A., too, many authors discussed this problem in "The Biology of Melanomas" published from the New York Academy of Sciences (1948).

According to Miescher's description, the frequency of so-called melanomalignoma, was 35 cases in 686 cases of cancer of the skin and the disease showed the initial symptom in the middle age, rarely in childhood (Darier and Civatte1) and in a suckling who was born from the mother of melanomalignoma (Weber, Schwarz and Hellenschmied2). In Japan, Kawanishi3) (1928) collected 44 cases and Ozaki4) (1933) 28 cases of melanomalignoma. Watanabe5) in our clinic collected 23 cases in Japanese literature from 1924 to 1938 of which three cases were reported histologically as cancer and others as sarcoma.

The locations of this disease can be distributed in the skin of whole body. On the head and face, they originate mostly from the lentigo. On the lower extremity especially on the foot, they present frequently ulcerated type and the subungual cases call attention as a specific variety. Recently Pack6) compared the frequency of the distribution of pigmented nevi with that of melanomas. According to his description, the regional distribution of pigmented nevi and melanomas over the skin is not exactly the same. Both tumors occur with considerable frequency on the face and neck, and equal frequency over the skin of the trunk. Pigmented nevi are not commonly found on the feet and on the genitals, but the frequency of melanomas in these specific locations is relatively high.

Their clinical and microscopical findings are different from each other corresponding to their locations. The prognosis is very various too. Some of them are very malignant: their metastasis is very fast and then there occur generalized melanomatosis and melanuria.

We want to report our recent cases with the object of histological and histochemical studies of melanin production.

Melanocarcinoma on the Face

The reports of the melanocarcinoma on the face are found frequently. In

* By Minor Ito and Yoshio Yoshida.
Japanese literature, too, there are many reports of melanoma originated from the lentigo or from the pigmented nevus on the face. Their prognosis is not so unfavorable. Most of them can be easily diagnosed as carcinoma by the histological examinations. As we think it unnecessary to discuss their pathogenesis especially here, we show five cases which were experienced by Itō, one of the authors, in his clinic of Kanazawa Medical College, Japan (Table XII).

**TABLE XII**

<table>
<thead>
<tr>
<th>Melanocarcinoma on the Face</th>
<th>Treatment</th>
<th>Histological findings</th>
<th>Localization</th>
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<td>Extirpation cured</td>
<td>Basal-cell carcinoma</td>
<td>Right external canthus</td>
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</tr>
<tr>
<td>Extirpation cured</td>
<td>Carcroid</td>
<td>Left nasolabial fold</td>
<td></td>
</tr>
<tr>
<td>Extirpation cured</td>
<td>Carcroid</td>
<td>Right medial canthus</td>
<td></td>
</tr>
<tr>
<td>Extirpation cured</td>
<td>Basal-cell carcinoma</td>
<td>Right upper eyelid</td>
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**Generalized Melanocarcinoma**

The metastasis of the malignant melanoma is very rapid and it shows often the generalized melanoma, in which the skin and many internal organs are invaded. According to Watanabe in our clinic, 7 cases out of 13 cases, in which the descriptions of the metastasis were clear, showed the generalized metastasis. Nevertheless, the detailed report of these cases is relatively rare. Way and Light reported a case, in which cutaneous metastasis was unusually extensive. Oka described a similar case and discussed especially the melanuria. The most interesting in these cases is the presence of the melanotic and amelanotic tumors. We experienced a similar case recently.

**Case Report:** A veterinarian, aged 65. First examination in 1951. He had remarked a smooth, pinhead-sized, blue spot on the anterior surface of the left thigh since childhood, which had produced no subjective symptom. About half a year before, he caught cold and injected himself on the place of previously described bluish pigmented spot. Next morning he noticed the reddening on the injected place. The reddened place around the pigmented spot so changed gradually into vitiligo macula that there are presented a Sutton’s leucoderma-like figure as a whole. At the same time, he noticed the leucoderma on the both sides of the preauricular regions, which enlarged gradually and reached about 3 cm in diameter. After several days from that time, he noticed numerous subcutaneous tumors, varying from 0.3 cm to 1 cm
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in diameter, on the left inguinal region and the anterior surface of the left thigh. These tumors enlarged in size and increased in number, spreading over almost whole body. On January 28, 1951, he had five fingertip-sized tumors extirpated on the left inguinal region and the part of Sutton’s leucoderma in the surgical department of our hospital. Since that time, the tumors on the whole body enlarged in size and increased in number more and more. On April 14, 1951, he came to our clinic. Status presents: A poorly nourished, anemic old man. Blood sedimentation rate (70–95), blood Wassermann’s reaction negative. There are the leucodermas on the both sides of preauricular regions and a pinhead-sized lentigo on the brow. Numerous subcutaneous tumors, varying from red-been to pigeonegg in size, are visible and palpable on the whole body, esp. on the left inguinal region. The majority of them does not adhere both to upper skin and to their bases. Some of them present bluish tone. Several fingertip-sized, hard lymph nodes on the right axillar, both sides of inguinal and left femoral region are palpable. Course: These tumors on the whole body especially on the left inguinal region enlarged in size and increased in number gradually. Some of them adhere to their upper skin where slight reddening are found. He complains severe, to the left leg running pain. The anemia and urobilinogen in the urine became more remarkable. But blood Takata-reaction and melanuria remained negative throughout the progress. X-ray examinations showed small quantity of effusion of the both sides of pleura and slight stenosis of the pylorus. On gastric juice examination, hypoacidity was presented. The occult blood tests of the gastric juice and feces were positive. Electrocardiogram in about 24 hours before his death, showed the figures of myocardinjury. He died in May 26, 1951.

The autopsy was performed and showed following findings: numerous tumors in the subcutis and muscles of whole body and multiple metastasis on the liver (amelanotic), spleen, mucous membrane of stomach, duodenum, jejunum, ileum and rectum, serous membrane of bladder, kidneys (but a few and amelanotic), thyroid gland, right lung, peri- and myocardium and lymph nodes of left pulmonary hilus, mesenterium, retroperitomeum, neck, left subclavicular, axillar and inguinal regions.

Histological and histochemical findings: 1) Sutton’s leucoderma on the anterior surface of the left thigh. On the leucodermal place, there are no change in the epidermis, no melanin granules in the basal cells and slight inflammatory changes but no chromatophore in the corium. The bluish pigmented spot, situating at the center of the leucoderma, presents no change in the epidermis and no pigment in the basal cells too. But there are nevus cell nests which are circumscribed in the reticular layer of the corium with slight round cell infiltration in their circumferences. These nevus cells contain relatively smaller pigment granules. These findings just correspond with that of Sutton’s leucoderma.

2) Amelanotic tumor on the left inguinal region. Epidermis normal. The basal cells were hyperpigmented. There are slight perivascular round cell infiltrations in the superficial subcutis and the tumor tissues clearly circumscribed in the deeper subcutis. Excepting the stromas, which consist of thin connective tissues with vascular dilatation and slight infiltration of round and a few other cells, the tumor are filled with irregularly sized, partially poorly stainable round, oval, polygonal and fusiform cells. Their nuclei present various quantity of chromatin, the figures of necrobiosis and mitosis in some places. These tumor cells present mostly the fascicu-
lar arrangements, but the strict examinations show the alveolar arrangements in a few places. There are no melanin granules, no dopa positive cells and no oxygen area by Unna's permanganate-methylgreen method in any places. These findings seem to be like the spindle-cell sarcoma at a glance, but the fact that the larger prickle cells present alveolar arrangements in some places suggests the basalioma or carcinoma. We cannot decide the conclusion only from these findings.

3) Melanotic tumor on the left pectoral region. Epidermis is somewhat thinned. The basal cells are highly hyperpigmented. In the deeper corium, there are groups of fusiform, stellate, round and oval cells. Their situations, morphologies and arrangements resemble to those of blue nevus. Nevertheless, we believe them to be the pigmented nevus cells. In the more deeper layer, spreading from the deepest corium to superficial subcutis, there are round and stellate cells which take the reticular or alveolar arrangements. These cells are so filled with melanin granules that their nuclei seem to be faded. In the more deeper layers, these cells change their arrangement gradually from alveolar to fascicular. From these findings, we know that the nevus cells change their arrangements with their situations. And then, we admitted that these nevus cell nests are the oxygen area by Unna's staining and present positive dopa reaction. But these two reactions are not so clear in the places where the cells are filled overflowingly with melanin granules.

4) Pinhead-sized lentigo on the brow. The basal cells are hyperpigmented. There are typical nevus cell nests in the superficial corium. These cells present positive dopa reaction. No malignant figure is found. We admitted that the nevus cells change their arrangements corresponding to their situation in this specimen too.

From abovementioned, we thought that congenital pigmented nevus was stimulated by the "Multin" injection and there occurred Sutton's leucoderma in the local and nevocarcinoma in whole body. The melanotic tumor cells presented positive dopa reaction and oxygen area by Unna's staining. The amelanotic tumor cells, on the other hand, showed negative dopa reaction and no oxygen areas. These facts reminded us of Greenstein's description. He believed that the melanotic melanomas, in contrast to the amelanotic melanomas, were characterized by the possession of 1) cyanide-sensitive tyrosinase, 2) cyanide-sensitive dopa oxydase, and 3) enzymatic system, or systems, which oxidizes $p$-phenyldiamine and which is largely insensitive to cyanide. And Cailliau attached great importance to $p$H in the field of the melanogenesis. From above we conclude as follows: the existence of amelanotic tumors does not always signify that the cases are taking very malignant course as some authors have believed, but it shows that the biochemical conditions in their fields, especially oxidoreduction potentialities, are insufficient for the pigment production.

Malignant Melanoma on the Sole

The melanoma is not commonly found in the darker races, but there are some reports of the cases on the sole where the pigmentation in the skin is very scarce (Bishop). In Japan, T. Ito (1906) reported a patient, aged 56, of malignant melanoma on the sole and since that time many authors described similar cases: Sekiba (47 y. female, 61 y. female), Ono (53 y. male), Kawanishi (66 y. male), Miyata (47 y. female, 58 y. male, 38 y. male), Uchida and Nokata (67 y. male, 56 y. male), Watanabe (67
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Case Report: A man, aged 67. First examination in 1947. His mother died of gastrocarcinoma. About one year ago, he noticed that a redbean-sized red spot grew on his right sole with no conscious cause. After two months, that spot broke down naturally and showed yellowish secrete. Then the bulla reappeared on the same place and soon light-yellowish tumor developed from the bottom of the bulla. This tumor enlarged gradually and became plum-sized presenting black tone. The patient came to our clinic complaining of the pain by walking. Status presens: General inspection showed no abnormality. Blood sedimentation rate moderately accelerated. There is a plum-sized, black, roughly papillary tumor on the frontal-half of the plantar arch of the right sole (Plate XI, Figure 43). The dirty, greyish white purulent secrete covers the elastic hard tumor which is limited sharply from the surrounding skin with red inflammatory halo. Right, one or two, hard femoral nodes can be palpated in fingertip-size. Course: Extirpations of the tumor and femoral nodes were performed and the patient took good progress. After about two years, he suffered from pleuritis exsudativa dextra and haemorrhagic effusion was removed several times by the punctures. He became cachexia gradually and died. From these facts, we think there occured the metastasis of the cancer. But he showed no melanuria throughout his progress.

Histological and histochemical findings: The major of elevated part of the tumor is the thickest stratum corneum, which contains many melanin granules everywhere. And the layers, situated immediately beneath the stratum corneum, consist of the nucleated cells with the homogeneous protoplasm. The stratum granulosum is scarcely found. As there are no intercellular spaces in the superficial prickle-cell layer, the cells are united closely each other and translate to the upper parakeratosis-like cell layer. The intercellular spaces and processes are slightly found in the deeper prickle-cell layer. The basal-cell layer is very irregular and shows figures of "théque (Darier)" in some places (Plate XI, Figure 44). There are the cells with clear protoplas or with vacuolization, which contain no melanin granules, and the flattened cells which contain melanin granules. The epidermal processes invade in the irregular form or drop down into the corium in the form of "Zellregen." When they show a transverse section, they present cancroidlike figure. These findings correspond with "Melanoma parakeratodes (Merenlender)." In the corium, the groups of polygonal or stellate cells show the alveolar arrangement. They have the great oval nucleus with the scanty chromatin and the melanin granules containing protoplas which shows in mostly the vacuolization. Some of these figures correspond with so called "ségrégation (Darier)." In the other field, however, these cells have the pyknotic nucleus and show the syncytial figure. Everywhere we find mitotic figures. These melanin containing cells take alveolar, reticular and fascicular arrangements. These arrangements transform their figures by their location in cutis: alveolar in the superficial corium, reticular in the more deeper and fascicular in the deepest (Plate XI, Figure 45). Thus the coexistence of "cellule sphérique" and "cellule rameuse" (Masson) is admitted. In other words, "mélanome endocrinien achromique" and "Spindelzellensarcom" are found in the same specimen. These findings correspond with "mélanoma dimorphe (Masson)." Examining these pigment cell nests by Mallory's staining, no fresh bluish fibril penetrates into them. Sudan III and Nile blue stainings show the lipoids, which
Malignant Melanoma

are double refractive by Nicol's apparatus, in the tumor-cell nests. (These points correspond with the observation by Kreibich.) From these facts, we know that these lipoids are cholesterins and the protoplasm which seemed to be vacuolar contained these substances. And then, by Unna's permanganate-methylgreen method, the tumor cells are stained intensely with methylgreen corresponding to the quantities of their containing melanin. From this, we know that there occurs the intense oxidation in these tumor cells. In the stroma of the corium, there are found generally the loose tissue where the slight round cell infiltration accompanies with a few plasma cells. The chromatophores increase in number at the places attached to nevus cell nests. From above findings, we diagnose this case as melanocarcinoma.

Melanoma on the Lips

Since Weber (1859), it has been admitted that when the melanomas were found on the buccal mucosa, they were seen most frequently on the palate. For examples, New (1929) collected 25 cases of melanoepitheloma on the palate at Mayo-Clinic and Fuhs & Kumer\(^1\) collected 31 cases of melanomas on the buccal mucosa from the literature, which were originated, without exception, from the palate and the maxillary dental alveolus. In Japan there are the reports by Kudo, Tsutsui, Nikaido, Kajitani, Tsuzuki and Iio. The cases on the lip were reported by Ono (55 y. male, 1918) and Takahashi (63 y. male, 1926). We experienced recently a case on the lip.

*Case Report:* A woman, aged 59, first came to our clinic in 1947. Her mother, six brothers and sisters and two daughters showed the ephelides. But other family history presents no abnormality. About fifteen years ago, she remarked a pinhead-sized black spot on the right side of the upper lip. But she took it for the ephelides and did not receive any treatment. After three or four years from that time, the spot increased in size and invaded into the red lip. Since January, 1947, she suffered from the bleeding when opens her mouth widely to take meals. Status presens: Build and nutrition normal. There are freckles on the face, forearms and trunk and the senile atrophy of the skin proper for her age. A jet-black spot on the right side of her upper lip distributed from the median line to the right labial commissure, taking its center in the red lip (Plate XI, Figure 46). It spreads to the skin over the upper lip in irregular form, where it presents more lighter browish tone than that of red lip. On the other side, the black spot extends on the mucous membrane inside the lip and shows the deep bluish color at its edge. The gingiva and the surface of the right second incisor present the deep black tone which don't fade even by severe rubbing (melanodontia). The boundary is very clear but slightly zigzag. At the red lip, this spot takes the papillary form and is covered by greyish white squama which can be stripped forcibly only with slight bleeding. The palpation shows somewhat thickness on these parts but no infiltration in the deeper place. She don't complain the itching. Only a left neck lymphatic gland can be palpated in pea-size. Blood pressure low for her age. Blood sedimentation rate slightly accelerated (56–82).

*Course:* Radiumtherapy was repeated four times with intervals of a month. The pigmentation was faded partially and the bleeding in the rhagadic places became better. After half year, when she came to our clinic, the tumor presented enlarging tendency. So the repeating radium therapy is being carried on.
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Histological findings: The epidermal thickness is very different by places. No hyperkeratosis. In some places, however, the melanin granules arrange themselves like the parakeratous nuclei. The stratum granulosum consists of five or six layers. In the deeper prickle-cell layer, there are many cells which involve melanin granules around their nuclei. The basal cells, consisted irregularly of cylindric and round cells, contain many melanin granules and, in some places, present the vacuolizations (Plate XI, Figure 47). The epidermal processes invade into the cutis very irregularly and present the figure of "Zellregen" in some places. In the corium, from the papillary to the reticular layer, there are round and stellate cells, whose protoplasms take so many melanin granules that their nuclei seem to be faded, in the alveolar or fascicular arrangements. From these findings, we know that these cells are the nevus cells. The changes in the stroma are considerable: dilated blood vessels, slight bleedings, infiltration of the round-, plasma cells, histiocytes and fibroblasts, and the chromatophores increased in number among abovementioned cells. Thus the findings are very complicated. We diagnose this case as melanocarcinoma nevogenes originated tardily from the ephelides or the abortive type of xeroderma pigmentosum.

Melanoma on the Pudenda

The melanomas on the pudenda are found more frequently in woman than in man. We experienced recently a case complicated with carcinoma on the labia pudendi.

Case Report: A woman, aged 53, came first to our clinic in 1946. She was operated twice, in 1929 and 1932, with the provisional diagnosis of uteruscarcinoma and became amenorrhoea since that time. In 1938, she was operated for the tumor on the anal region and the swelled right inguinal glands. Since January, 1938, she remarked a little-fingertip-sized, dark red tumor on the right labia majora with stiching pain. Salvarsan injections brought about no improvement. The tumor and the right inguinal glands enlarged more and more. Status presens: Blood Wassermann's reaction (-), blood sedimentation rate (83–102). There is a cockscomb-shaped tumor on the right labia majora and its surface is papillary, macerated greyish or ulcerated with light red tone. It is covered generally by the purulent secrete and very stinking. On the anal region, a dark red hemorrhoidlike tumor is found. They are palpated elastic hard as whole. She complains a slight pain by compression. The border is considerably sharp. Several, hard, right inguinal glands are palpated in thumbtip- to pigeonegg-size. On the left labia majora, no swelling and infiltration are found. When the tumor on the right labia majora is compressed to outside, the atrophic, hard vaginal orificium and wall can be palpated and the latter is ulcerated painfully in some places. Near to the left commissura labiorum posterior, a halfring-shaped, bluish black, narrowly elevated region is palpated somewhat hard (Plate XII, Figure 48). The skin in this region presents the lightred tone and is thickened slightly, but there are no infiltration in its deeper part and no pain by compression. Course: After about a week from the extirpation of the tumor on the right labia majora, the halfring-shaped melanoma on the left side lost its black tone. This tumor was extirpated and observed microscopically. Since that time, there was favorable progress for short time, but the relapse occurred soon. The extirpation, X-ray- and radium-therapy
were performed energetically for about eight months. But there is no favorable effect and the patient was discharged. Her family reported her death soon after that time.

Histological findings: The tumor on the right labia majora presents a typical figure of basal-cell carcinoma and, in some places, Bowen's so-called "clumping cells" are found. The suddenly disappeared tumor on the left side presents next findings. Epidermis very thickened, a few epidermal processes found, and horny layers not so clear with one or two parakeratotic layers. Attaching to two or three granular layers, there are the prickle cells, which so lose their prickles that they are close each other. They are not so good stainable and their protoplasms show the vacuolizations everywhere. In the deeper prickle layer, there are larger, round, chromatin-rich nuclei. They became gradually like the basal cell and finally they transit to the basal-cell layer, which consists of cylindric palisade cells and which presents no abnormal change such as vacuolization. These findings correspond with those of the basalioma. In some places, however, the cells with fusiform nuclei and gigant cells as in Bowen's disease are found. This finding corresponds with that of the tumor on the right labia majora. The basal cells involve a few melanin granules, but some cells in the superficial Malpighian layer involve the dendritic or massive melanin granules. In the corium, a few chromatophores are found. Thus, there is no figure of melanoma.

The prognosis of melanoma is very various and there are some reports showing the natural cure (Ribbert, Borst, Cange and Deboucher). Bertier-Weissenbach and Darier reported the cases in which the metastatic tumors became smaller and finally disappeared by the extirpation of the chief tumors. We believe this patient as similar case.

Panaris Mélaniques

Melanomas on the fingertips or the nailbed were observed first by Hutchinson in 1881 and the French school, Dubreuilh and Darier, named them "panaris mélaniques" or "tourniole mélanique" as specific type. Since that time, Specht and Chauvenet-Dubreuilh collected similar cases from the literature. Adair, Pack, and Nicholson at Memorial Hospital counted 26 cases of the subungual melanoma out of 218 cases of melanoma. Womack, taking his materials from the patients of Barnes Hospital in St. Louis, reported that this disease was found in 15% of all melanomas. The cases in the Black races were reported by Adair-Pack, Bauer-Dickson and Jarman. In Japan, since the first report by Kumagai in 1906 (62 y. female), Inoue (51 y. female), Kawamura (57 y. female), Miyata (51 y. female) and Yano-Nohara (26 y. male) reported their cases as the melanoma on the fingertip. These cases occurred frequently in over fifty years of age, in women and especially on the thumbs. From these points, it has been thought that the traumas play a great rôle as the accelerating causes.

Case 1.—A woman, aged 60. First examination in 1942. Her elder sister died of gastrocarcinoma, but no other family history. Since three years, she remarked a red-bean-sized lentigolike tumor on the nail side border of left thumb. Spreading to the volar side of the thumb, it enlarged gradually and became easy to bleed. As the nail side border suppurated with pain about a month before, the incision was performed. Since that time, the tumor added the speed of its enlargement. Status
presens: Healthy woman at first sight. The swelling of the aorta and hypertension were found, but blood Wassermann’s reaction was negative. Slight albuminuria but no melanuria. There are excoriated, irregular-sized, bluish black spot, taking its center in the nailbed of the left thumbtip and extending from the dorsal to the volar side (Plate XII, Figure 49). This looks as if an Indian-ink permeates under the epidermis. These places are slightly elevated and bordered clearly from the circumference. One or two pustules are found on the nail side border. The nail plate, which is thickened markedly and loses its polish, shows deep black longitudinal bands on both sides (melanonychia), and retains its natural color only in the center. But there is admitted no infiltration, only slight roughness in all places. She complains of pain by moving the nail-plate. A plum-sized enlarged node is palpable with slight pain in the left axillar region.

Histological and histochemical findings: Stratum corneum and rete Malpighii thicken highly corresponding to the location of the fingertip. At the center of the lesion, there are fusiforme, nonnuclear, pigment granules containing cells, which are circumscribed in some places and which are localized horizontally as fish scales. But no parakeratosis is found. Stratum granulosum consists of four or five layers. The prickle cells show the perinuclear vacuoles everywhere. The basal cells, which show the irregular form and arrangements, change themselves into foamy, vacuolar form at the top of the eidermal processes. And, attaching to them, there is the figure of “Akantholyse.” Moreover, there are some basal cells, which dropped off in the figure of so-called “Zellregen” attaching to the epidermis or separating in the cutis. The latter cells, surrounded by the connective tissue, present the nests of round or stellate pigmentcells. Especially in the little nests, we admitted the figure of so-called “cellules claires (Masson)” or “Zwillingszelle (Merkel-Ranvier).” The chief change in the corium is the remarkable increase of the pigmented cell groups, which invade into the papilla from the subpapilla and whose pigment granules are grosser and show intense argentaffinity (Plate XII, Figure 50). These cells present the fusiform, stellate or round form and are filled with so much pigment granules, that their nuclei cannot be found. These pigments are negative in the iron-reaction, fade slightly by the 24 hours’ procedure of H₂O₂ and lose the black color almost completely by 48 hours’ procedure. From these facts, they are admitted as melanin granules. These pigment cells are found in groups around the capillaries or the nests of the epidermal cells, which are migrated from the epidermis to the corium. But their arrangements don’t always show the alveolar structures as in the nevus cell nests, where the melanin granules are rich in the peripheries but a few in the centers. According to Bielschowsky-Maresch’s staining (Plate XII, Figure 51), the pigmentcells are encapsulated by the argentaffin fibers and the close relationships between them and the argentaffin fibers around the capillaries in the center can be admitted. But these argentaffin fibers don’t invade into the places, where the vacuolar changes are presented in the top of the epidermal processes, and into the epidermal cells dropped off into the corium. The capillary-intimas in the papilla, where the pigmentcell infiltrations are found, are thickened so highly, that their spaces become very narrow and the subpapillary blood vesseles are dilated and filled with blood cells. Everywhere the moderate infiltrations of little round cells and histiocytes are found. The nerve fiber staining by Bielschowsky-Seto’s method shows that there are rich in the nerve organs corresponding to this
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location, fingertip. Wagner-Meissner's, Vater-Paccini's corpuscles and many nerve fibers are admitted. Many thicker nerve fibers and fine vegetative nerve fibers, which intertwine with the blood vessels, penetrate the pigment cell infiltrations. Moreover, the periphery nerve fibers invading into the epidermis from the papilla are found everywhere. And then, some of nerve fibers in the stratum reticulare are thickened fusiform or braid-like in shape and some of them in the deeper reticular layer present a glomerular form, so that they are admitted as the little nest of neurino-fibroma. But there are no changes anywhere as "corpuscles naeviques" and "lames foliacees," on which Masson based his neuroectodermal theory of nevus cell. Examining the relationships between these nerve fibers and the pigment cells, we get next findings: Meissner's corpuscles are encapsulated with the pigment cells but no argentaffin granules are found in the corpuscles, and, around the transverse section of nerve bundles in the stratum reticulare, there are fusiform pigment cells but they don't invade into the nerve fiber sheaths.

Case 2.—A woman, aged 46, had a trauma on the left thumb about five years ago. This region was suppurated about two years ago. Repeated incisions brought about no improvement. On examination in Jan., 1951 she showed so-called panaris melaniques on the nail and endophalangeal region of left thumb and some symptoms of mental disturbance. She died in Oct., 1951. The autopsy presented the metastasis of the melanoma on the cerebrum, ribs, omentum majus, gallbladder, stomach and ileum. In the specimen obtained from the volar side of left thumb, typical nevus cell nests could be found. Therefore we diagnosed this case as melanocarcinoma. (The details will be reported another day in collaboration with Yamamura, department of psychiatry, Hirosaki University.)

Milian pointed out the fact that there coexist both histological findings of melanocarcinoma and melanosarcoma. Our first case seems to present such findings as Milian described. But we could diagnose distinctly the second case as nevocarcinoma. We believe that the majority of panaris melaniques is melanocarcinoma, though their histological diagnosis is very difficult sometimes.

Mélanome Malin Mésenchymateux or Melanosarcoma

In 1925, Darier described three cases of malignant melanoma originated from the blue nevus. This disease is very rare and, inspite of its designation (melanoma), it is not tumorous but the bluish or slate-blue flat spot, in which the black or deep brown shrapnel-like nodules are dotted and somewhat roughly palpated. It malignizes suddenly in the puberty. The locations in Darier's three cases, were auricular, mandibular, neck, scapular and pectoral regions. The regional lymph nodes swelled as in inflammatory changes, but when they presented the metastasis-like changes, the patients took frequently the unfavorable prognosis. The progress, however, are gradual in many cases and some of them are cured with electrocoagulation. And so we cannot conclude all of them to be malignant.

Histological findings: The fusiform, stellate and long fibrous cells involving the pigment granules are found in group among the connective tissues or around the blood vessels in the deeper corium as in blue nevus or Mongolian spot. From these findings, we think that this is just mesenchymal melanoma and must be dis-
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tinguished from the nevogeneous melanoma as described above.

But many cases reported as melanosarcoma in Japan, we believe, are not always limited strictly in the mélanome mésembryomeux in the sense of Darier. For example, the malignant melanoma originated from the fasciculated form of nevus cell has been described as melanosarcoma. On the other hand, since Stranz, the cases, in which the blue nevus and the pigmented nevus were complicated, have been reported. Recently Kawamura described also a similar case in Japan. When these cases become malignant, the histological findings, we believe, become more and more complex. We know a good example of these cases. That is a case reported by Ozaki at the pathological laboratory of our University in 1933. The case is as follows. A man, aged 52, presented an extensive blue nevus which spread on the right forehead, temporal and parietal regions and which was complicated with the shrapnel-like black nodules. Showing generalized metastasis and melanuria, it took malignant progress and he died. The biopsy was performed. Ozaki, from the point of Ribbert's chromatophore theory, diagnosed his case as melanosarcoma. We could examine this preparations by the kindness of the pathological laboratory and we found that there coexist both typical findings of the blue nevus and the malignized pigmented nevus with the alveolar or fascicular arrangements in the original location on the skin. From these findings, we cannot agree to make the case as melanosarcoma. We think it proper to diagnose the case as the complicated form of the blue nevus and the melanocarcinoma. To say the least, this case does not correspond to the melanosarcoma in the Darier's sense.

SUMMARY

From abovementioned, we conclude as follows:

The malignant melanoma, whose majority had been considered as the melanomasarcoma by many authors, is melanocarcinoma with a few exceptions.

The malignant melanoma originated from the blue nevus is melanosarcoma as Darier described. But we must not forget the facts that the nevus cells change their arrangements from alveolar to reticular or fascicular corresponding to their situations and that some cases show the coexistence of pigmented nevus and blue nevus. When these cases became malignant, the strict examinations are necessary for their diagnosis.

The existence of amelanotic tumors in the malignant melanoma does not always signify that the cases are taking very malignant course, but it shows that the biochemical conditions in their fields, especially oxidoreduction potentiality, are insufficient for the pigment production.

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