

## LENTIGINOSIS PROFUSA SYNDROME (MULTIPLE LENTIGINES SYNDROME)

### II. *Histological Findings, Modified Crowe's Sign, and Possible Relationship to von Recklinghausen's Disease*

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*Abstract.* In a patient with lentiginosis profusa syndrome, multiple melanotic spots studded the axillary vaults. Histological study of one of these spots and of typical-sized (2-4 mm) pigmentary lesions of the abdomen and back did not reveal progression to nevocytic nevi. However, one of the occasional large (several cm) pigmentary lesions exhibited melanocytic junctional theques and "dropping off" of such nests into the dermis (analogous to nevocytic changes that may occur in the café-au-lait spots associated with neurofibromatosis). The axillary melanotic macules observed in lentiginosis profusa were comparable to those of von Recklinghausen's disease (Crowe's sign) in distribution and size, but were darker in hue and hence referred to as a modified Crowe's sign.

The 19-year-old woman of Italian descent in whom the clinical investigation reported here was performed, together with her 52-year-old mother who also has the lentiginosis profusa syndrome, have been described in some detail in previous reports (22, 24). Collective manifestations in both patients included profuse lentiginosis, hypertelorism, defective oculomotility, deafness, cardiopathy and dermatoglyphic aberrations. These manifestations are characteristic of the syndrome (11). Henceforth, reference is made only to the daughter.

#### CLINICAL CUTANEOUS FEATURES

The lentigines developed from early childhood through puberty. (Subsequently in this article, a broad definition will be recounted for the term *lentigo* to justify its use here and in the designation of the disorder (22, 24)). A vast number of lentigines covered the whole body-surface but mucous membranes were spared. The lesions were irregular in shape and the great majority ranged in size from pinpoint dots to 5 mm in longest

dimension. A few pigmentations were much larger, up to 5 cm in major axis (Fig. 1). The very smallest lesions were light tan; those over a mm or two were blackish-brown and therefore cosmetically disfiguring.

The axillary vaults were studded with lentigines (Fig. 2). There was no symmetry or equal density of lesions, when comparing one axilla with another. In addition to the macular lesions, there was one brown pedunculated lesion 2 mm in diameter and of 2 mm elevation in the left posterior axillary line, and a similar tag-like structure on the left flank.

A further cutaneous feature was the presence of 10 dermal nodules. The majority (8) were found on various portions of the upper extremities, 1 was at the medial base of the left breast, and 1 was at the lateral aspect of the left patella. The first nodule was noted when the patient was 9 years old. Since then, additional, asymptomatic, slowly enlarging nodules appeared at the rate of about one a year. The nodules varied in size from 4-15 mm in major axes. The larger ones were fusiform and aligned parallel to dermatomal projections.

#### HISTOLOGICAL STUDIES

Hematoxylin and eosin stained sections were prepared from all biopsies. Some sections of pigmented lesions were also treated by silver staining to gain an appreciation of the number of epidermal melanocytes.

Punch excisional biopsies were performed on 3 typical-sized lentigines in the 2-4 mm range located on back, abdomen, and in the left axillary

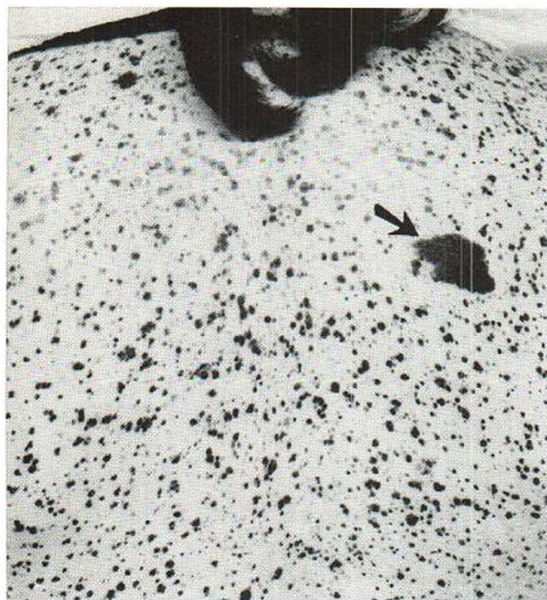


Fig. 1. Astronomical multitude of lentigines on the back. The large pigmented lesion (arrow) over the scapular area was examined histologically.

vault. The pedunculated lesion in the posterior axillary line was snipped off for sectioning. 2 mm punch biopsy specimens were removed from the central portions of large pigmentations on the back and abdomen (Fig. 1). Finally, 2 dermal nodules were excised from the left upper extremity.

Microscopically, the 3 typical-sized lesions and the central portion of the abdominal pigmentation had certain features of lentigines. Melanin was abundant in the epidermis and concentrated in the basal layer. Numerous dendritic melanocytes were located in the epidermis. The degree of epidermal rete ridge elongation and clubbing varied with the site and ranged from nought to noteworthy (Fig. 3). In the superficial dermis there were plentiful melanophages accompanied by a banal chronic inflammatory infiltrate.

Part of the central portion of the large pigmentation on the back had the microscopic appearance of lentigo with prominently elongated epidermal rete ridges; nearby, however, there were well developed melanocytic junctional theques and "dropping off" of melanocytic nests into the superficial dermis (Fig. 4). It was evident that the lesion had progressed to become a bona-fide nevus. The pedunculated lesion had the microscopic fea-

tures of a compound nevocytic nevus and consisted of melanized epidermis, junctional melanocytic theques, sheets of typical dermal nevocytes extending from the epidermis well into the dermis, melanophages, and a moderate inflammatory infiltrate.

Microscopic examination of the 2 nodules revealed sheets of cells dissociating the dermal collagen fibers. The cells contained small dark-stained nuclei and granular eosinophilic cytoplasm typical of granular cell schwannoma (24) ("myoblastoma"). (See appropriate photomicrograph in ref. 24.)

### COSMETIC TREATMENT

The histologic findings divulge a rationale for a cosmetic therapeutic approach by external means. The 3 typical-sized macular melanotic lesions examined microscopically (and a similar lesion excised from the back of the affected 52-year-old mother) did not develop actual theques of epidermal melanocytes to serve as precursors for deeper, dermal, nevocytic encroachment. Presumably, a process that would remove such lesions to the depth of the deepest projections of their rete ridges would eradicate these cosmetic blemishes.

Two years ago, Dr Norman Orentreich performed a facial dermabrasion on the patient (22). Prior to this treatment, the facial macular pig-

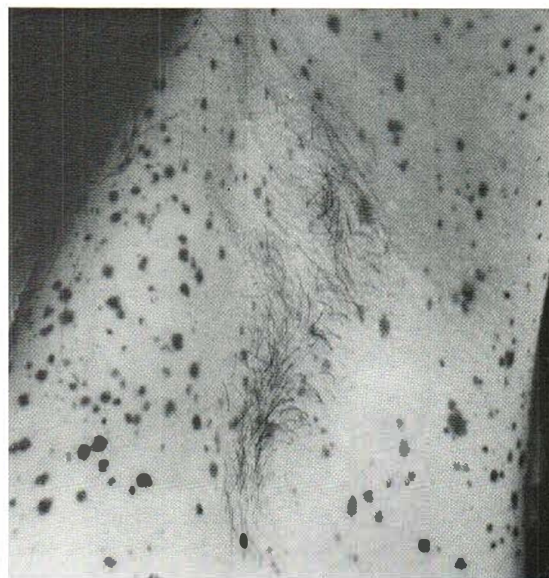


Fig. 2. Lentigines in axilla and surrounding regions.



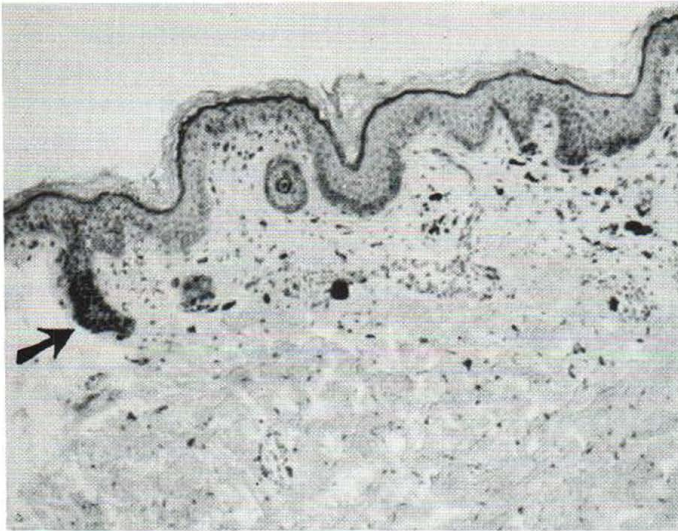


Fig. 3 a. Axillary lentigo: The epidermis showed increased melanization, concentrated in the basal layer. The superficial dermis was occupied by melanophages. The epidermis was undulated but there was no prominence of actual ridging except for the one, long, heavily melanized rete ridge near to the end of the section (arrow). Hematoxylin-eosin,  $\times 70$ .

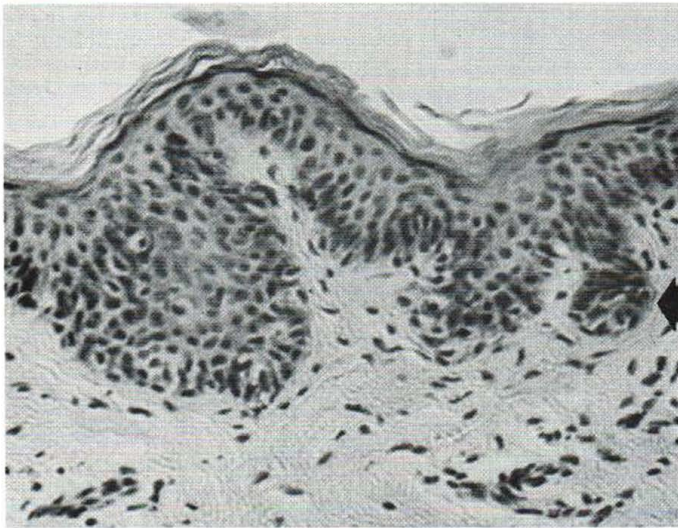


Fig. 3 b. This specimen from the center of a large pigmented lesion on the abdomen showed a little more development of rete ridges, including a club-shaped rete ridge near the edge of the section (arrow). The epidermis, especially the basal layer, was heavily melanized, and in the dermis there were plentiful melanophages. (Also see appropriate photomicrograph in reference 24 for still better developed club-shaped rete ridges.) Hematoxylin-eosin,  $\times 270$ .

mentations were of the usual size range of 5 mm or smaller. Though a relatively small percentage of the lesions recurred, the overall cosmetic improvement to date is notable (Fig. 5). The reappearance of some pigmentations may be due to some of the deepest rete projections not being removed by the initial dermabrasion; hence allowing these lesions to regenerate. The elongation of the rete ridges does vary with the lesion. Another explanation for recurrences is the possibility that a few of the *typical-sized* macular pigmentations were actually nevi that generated dermal nevocytes to a depth beyond usual dermabrasion, though our sampling of 3 lesions of this size-range (4, counting the mother's) did not sub-

stantiate this theory. Of course, coincidental nevi, unrelated to the condition, may have played a role. As described previously, pedunculated and unusually large pigmented lesions can be nevi.

In exposed areas not amenable to favorable cosmetic results by dermabrasion, such as on the ears and neck, lentigines were treated by light electrodesiccation (22). The treated areas were thus lightened to a whitish (hypopigmented) hue, making them less noticeable though not homogeneous with the surrounding normal-appearing pinkish skin. The principle for destruction of the lesions, whether by electrodesiccation or other modalities (e.g. cryotherapy), is the same as was discussed under dermabrasion.

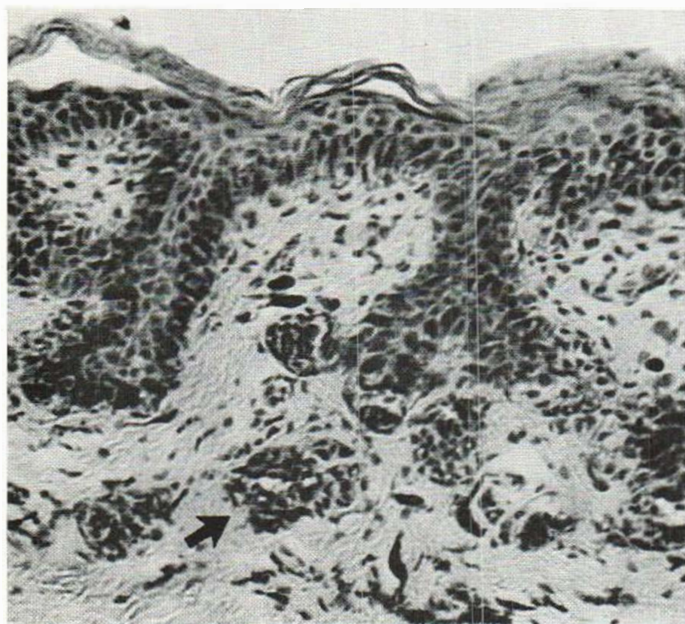


Fig. 4. Histological section from center of large pigmentation illustrated in Fig. 1. Junctional melanocytic theques have organized and there was "dropping off" (arrow) into the dermis. The neighboring rete ridge was prominent and heavily melanized but did not contain theques. Dermal melanophages were abundant. Hematoxylin-cosin,  $\times 245$ .

#### MODIFIED CROWE'S SIGN

The *clinical* sign of freckle-like pigmented macules in the axillary vaults has been considered pathognomonic of von Recklinghausen's disease (6, 21). Among 223 cases of proven neurofibromatosis, Crowe found that 45 patients had axillary "freckling" (6). He later examined 30 more patients with

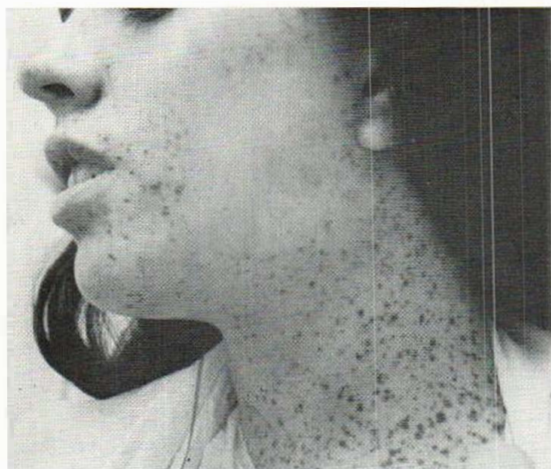


Fig. 5. Prior to therapy, the skin on the side of the face resembled that of the lower portion of the neck. The face was treated by dermabrasion and lentigines of the submental region and of the upper antero-lateral portion of the neck were electrodesiccated. On the side of the face not shown, there was more recurrence of lentigines.

the disease and found 10 more with the axillary sign, giving an overall total of 55 out of 253, or about 22% of the cases with "Crowe's sign". Crowe further observed that normal persons who have freckling have clear axillary vaults, the ephelides stopping at the anterior and posterior axillary lines; that people with generalized lentigines may show increased pigmentation and an occasional lentigo in the axillae; and that among 6 856 normal individuals, not one had axillary freckling.

Use of the term *freckle* (or *ephelis*) for the small cutaneous pigmentary lesions of von Recklinghausen's disease (4, 6, 7) is probably *not* correct. In this disease, apart from the axillary sign, small pigmentations are not uncommonly found in profusion and in widespread distribution on the body-surface (7, 21). In his study of café-au-lait spots of neurofibromatosis, Kawamura (13) employed the dopa reaction to demonstrate an increase *in the number* as well as in the activity of melanocytes. Benedict et al. (3) calculated the number of melanocytes per  $\text{cm}^2$  of café-au-lait spots (also using the dopa technique) and in most (but not all) instances found a statistically significant increase compared with the average for normal skin of the same region. If the small pigmentary lesions follow suit, as the study of one such lesion by Johnson (12) indicates, then there is reason for *not* calling them freckles, since the common



freckle does *not* show an increase in the number of melanocytes (17). Moreover, clinically, the small pigmentations of neurofibromatosis differ from freckles by their more widespread distribution over the body-surface and their non-dependence on sunlight to render them visible. From what is known, the small lesions are best considered miniature café-au-lait spots (12).

Lentigines are characterized by an increased number of epidermal melanocytes (17). But the often-applied histological criteria of elongated and club-shaped rete ridges will have to be waived (23) if the term *lentigo* is to be more correctly applied in lentiginosis profusa, since many pigmentations will not show this change. Pinkus & Mehregan (20) indicate that in lentigo simplex there is not always accentuation of the rete ridges. Etymologically, *lentigo* is derived from the Latin word for a lentil-shaped spot (16), and clinically, the cutaneous lesions in lentiginosis profusa roughly fit under this original heading, for lentil seeds are 5 mm or less in diameter but are roundish and with moderately smooth borders. The loose criteria herein applied to the designation *lentigo* are the above gross morphology and the histological impression of an increased frequency of melanocytes. By this definition, the small spots of neurofibromatosis may be considered a type of lentiginosis, but describing them as miniature café-au-lait spots is more informative by indicating their light coffee and milk (5) color (vs deeper hue in lentiginosis profusa) and by implying their relationship to neurofibromatosis.

The axillary pigmentations observed in lentiginosis profusa were comparable to those of von Recklinghausen's disease in distribution and size, but were much darker. Hence, this phenomenon is being referred to as a *modified Crowe's sign*. Possibly, in patients with lentiginosis profusa syndrome having low cutaneous expressivity (11, 24), the spots may be of light hue and the axillary changes may defy clinical distinction from those of neurofibromatosis.

A case of pertinent interest was reported by Apted (2): 9 granular cell schwannomas in a 10-year-old girl who also had multiple, small, "freckle-like" (non deeply pigmented) melanotic macules on her face, trunk, limbs, and in each axilla. Since Crowe's sign was considered pathognomonic of von Recklinghausen's disease, Apted suggested that his patient had a diathesis for this disorder

and that this lent support to the neural origin hypothesis (9, 10, 17) for the granular cell tumors. In view of the axillary lentiginosis and granular cell schwannomas in the patient described in this article, it also seems reasonable that Apted's patient may have some connection with the lentiginosis profusa syndrome. Indeed, circumstantial evidence suggests that the lentiginosis profusa syndrome and von Recklinghausen's disease may in some way be related.

#### RELATIONSHIP TO VON RECKLINGHAUSEN'S DISEASE (NEUROFIBROMATOSIS)

The lentiginosis profusa syndrome and von Recklinghausen's disease share the following identical, similar, or possibly related features:

1. Autosomal dominant pattern of inheritance (11, 24).

2. Increased incidence of general somatic and mental retardation, and delayed, incomplete or aberrant sexual development, compared with the population at large (4, 11).

3. In addition to generalized skeletal retardation, certain malformations, e.g. kyphosis (11) and scoliosis (15), occur with inordinate frequency.

4. Small-sized (<5 mm) cutaneous melanotic macules, profuse, widespread and including the axillary vaults: In lentiginosis profusa, the lesions tend to have a much more intense hue and thus dramatically alter the appearance of the individual.

5. Large (>1 cm) cutaneous melanotic macules: The café-au-lait spots of neurofibromatosis may develop into nevi (1), as may the more deeply pigmented counterpart in lentiginosis profusa. The café-au-lait spot is often oval and with fairly smooth borders (as many descriptions intimate (4, 7, 21)), but not always; Benedict et al. (3) demonstrated the unreliability of these configurational criteria for individual cases in differentiating the café-au-lait spots of neurofibromatosis from the large pigmentations associated with Albright's syndrome. The latter were traditionally thought to be distinguishable because of their irregular cartographic shape and serrated margins. In cases of lentiginosis profusa seen by the author, the large pigmentations tended to be irregular in shape and margination.

6. Cutaneous tumors of neuroectodermal origin:

In lentiginosis profusa, the patient described here had multiple granular cell schwannomas (24). Apted's case (2), previously discussed, may be a second example of this phenomenon. Many proofs, anatomical, histochemical and electron microscopic (9, 10, 17), have been offered to support the schwannian cell histogenesis of these tumors. In cutaneous neurofibromas, the histochemical finding of cells with nonspecific cholinesterase activity (26) substantiated, on the basis of function, what early studies suggested on the basis of structure: namely, that neurofibromas are, at least in considerable proportion (17), of neuroectodermal (probably schwannian cell) origin. In *in vitro* tissue culture preparations of cutaneous neurofibromas, Klaus & Winkelmann (14) confirmatively identified cholinesterase-positive schwannian-type cells.

Fialkow et al. (8) recently studied 14 inherited neurofibromas in 2 unrelated negro women heterozygous for the A and B genes at the X-linked glucose-6-phosphate dehydrogenase (G-6-PD) locus. Each neurofibroma had dual populations of enzyme phenotypes (compatible with Lyon's hypothesis) thereby intimating that hereditary neurofibromas are of multicellular origin. (For unicellular histogenesis, a single uniform population would be expected.) The above duality in every one of the 14 neurofibromas studied intimates that the initial tumorigenic event either affects a relatively large number of cells simultaneously or that it alters one or a few cells and this alteration subsequently influences the pattern of growth in many neighboring cells.

7. Analogous theories of causation: Nicholls (18, 19) postulated that in von Recklinghausen's disease, if a particular change in a cell differentiated from neural crest cells initiates pigmentary or tumorous (neurofibromatous) lesions, according to the cell type, such change occurring in the common stem cell should produce both lesions (compatible with clinical observations). The plethora of nervous system anomalies of von Recklinghausen's disease are well known and need not be recounted. Analogously, in the lentiginosis profusa syndrome (24), a change in neural crest stem cells would account for the pigmentary lesions and the granular cell schwannomas. Further indications of an underlying factor relating to the nervous system are the mental deficiency, oculomotor defects, neural deafness and cardiac con-

duction defects that in variable degrees of expressivity constitute a major part of the syndrome.

Apart from a possibly close-knit relationship to neurofibromatosis (25), the lentiginosis profusa syndrome has been previously compared to various other genopathies (24). The constellation of features shared in common with Noonan's (pseudo-Turner's) syndrome is impressive.

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