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THE NATURAL HISTORY OF THE PIGMENTED NEVUS; FACTORS OF AGE AND ANATOMIC LOCATION*

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The pigmented nevus undergoes a peculiar pattern of development and structural differentiation throughout life. This was first described by Unna^{1,2} and little has been added to his original observations. Although different types of pigmented nevi are distinguished, many actually represent the same process in different phases of development.

Recently, stress has been laid on the "junctional" or "dermo-epidermal" nevus, in which there is proliferation of cells in the epidermis and at the dermo-epidermal junction. Traub and Keil,³ in agreement with Kaufmann-Wolf,⁴ regard this proliferation as "potentially malignant (precancerous)" whether it arises early or late in life. To Allen⁵ it is the "most precarious of the precancerous lesions" of the skin. Allen,⁶ however, points out that this special significance is to be attached only after puberty. Sachs, MacKee, Schwartz, and Pierson⁷ distinguish the junctional nevus from the "intradermic nevus" or common mole, and consider it to be the only forerunner of nevocarcinoma. Miescher⁸ does not agree with Kaufmann-Wolf that proliferation of cells at the junctional zone is in itself evidence of malignant neoplasia. He regards it as part of "nevogenesis" and precancerous only in the sense that the primary lesion of melanoblastoma[†] is an alteration of this form of proliferation. Some of these authors present objective evidence in support of their views, but more is needed.

The full significance of the histologic features of nevi and melanoblastoma can be learned only after certain data are gathered and cor-

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† Throughout this paper the term melanoblastoma designates the malignant neoplasm for which nevocarcinoma, malignant melanoma, and malignant melanoblastoma are considered by some to be acceptable synonyms.—*Editor.*

relations made. First, the usual appearances and extent of variation of ordinary nevi of patients of all ages and in all anatomic sites are to be determined. Second, comparisons are to be made with proved melanoblastomas. Third, it remains to be determined that histologic evaluation affords reliable information as to the eventual outcome. This investigation undertakes the first of these steps.

The older literature on the histologic appearance of nevi in different age groups and the origin of the nevus cell has been well covered by Fox,⁹ Fick,¹⁰ Frédéric,¹¹ Gans,¹² and Riecke.¹³ Theories of epithelial, endothelial, connective tissue, and neural origin were proposed. The more systematic analyses of developmental changes throughout life were by Unna^{1,2} and other supporters of the theory of epithelial origin of nevus cells.

In presenting his arguments for the neural nature of nevus cells, Masson¹⁴ again pointed out differences between incipient and old nevi. However, his work and that of Feyrter¹⁵ and of John¹⁶ have been concerned largely with cytologic detail, and comparatively few nevi were reported. Among his 10 cases, Feyrter described a nevus of a patient 1 year old. The remainder were in adults. John based most of his impressions of the appearance of young nevi on a case of leukoderma acquisitum centrifugum of short duration, although the patient was an adult. In his other cases the age varied. The youngest age specifically stated was 12 years. The larger series of Miescher and von Albertini¹⁷ and of Montgomery and Kernohan¹⁸ included nevi of subjects of various ages, but no correlation was made between the appearance of the nevi and the age of the patients. The recent article of Spitz¹⁹ contributes valuable information concerning the nevi of childhood but does not pretend to be an inclusive decade-by-decade analysis.

METHOD AND RESULTS

Two hundred nevi, considered to be benign both clinically and histologically, were studied. Representation of various ages and locations was sought for, but otherwise the selection was random. When multiple nevi were excised from one patient, each was considered separately. Blue nevi were omitted.

About ten lesions previously designated as pigmented nevi were reclassified as lentigines. They were from patients of all age groups and, although the distinction of lentigo from nevus is not clear, they were not included in the series. They consisted of hyperpigmented epidermis with occasional clear cells scattered along the deeper zone. There were

no well defined intra-epidermal clumps and no nevus cells in the corium. Occasional melanophores were present, however.

The nevi were subdivided as to the age of the patient and as to the following regions: (1) head and neck, exclusive of conjunctiva; (2) trunk, including external genitalia and perineum; (3) shoulders, arms, buttocks, and thighs (designated as the proximal parts of the extremities); (4) forearms, hands, legs, and feet (designated as the distal parts of the extremities).

Routine surgical material was used. Descriptions and opinions are therefore based on the appearance of one or a few planes of section. While serial sections might disclose certain details, as for example sparse foci of junctional proliferation, the method pursued is adequate for comparisons and for the establishment of a trend in a series as large as this.

Clinical records were examined and as many cases as possible were followed for different periods of time. Histories concerning nevi are usually inadequate and some of the moles were removed incidental to other surgical procedures. Data based on the patient's ideas of duration were obtained in 87.5 per cent of cases, concerning growth of nevi in 87.5 per cent, and follow-up from the time of the surgical excision to the time of the analysis was successful in 88.5 per cent.

In 89.7 per cent of cases in which there was information, the nevus was said to have been present from birth or childhood, or in adults for an indefinitely long time. Therefore, the trends presented in the following discussion are to be correlated not only with the age of the patient but also approximately with the duration of the nevus. The exceptions are analyzed in a later section.

Of the 177 cases with follow-up, there was recurrence in 3 cases but there was no subsequent growth nor was there histologic evidence of melanoblastoma. Nine patients died subsequently, one of carcinoma of the stomach, 2 of carcinoma of the breast, one of heart disease, one of pemphigus, one of alcoholism, one was killed in action in World War II, and for 2 the cause of death was unstated. Follow-up was carried out on one case for 1 month, 2 for 5 months, 2 for 6 months, 28 for 1 year, 18 for 2 years, 8 for 3 years, 20 for 4 years, 60 for 5 to 9 years, 23 for 10 to 14 years, and 15 for 15 to 19 years.

Special attention was directed toward size and shape of the nevi, junctional and intra-epidermal cellular proliferation, mitotic figures, distribution of nevus cells, presence of fibrillar and nerve-like elements, pigmentation, multinucleated cells, inflammation, vascular changes, and

miscellaneous observations. Correlation with certain clinical features was made.

Size and General Configuration. The nevi were segregated as narrow stratified, broad stratified, and bulky according to the general unmagnified view of the microscopic section. By "narrow stratified" is meant a slender zone of cells in the epidermis or corium lying parallel to the skin surface. Approximately 0.6 mm. was considered the critical width between narrow and broad. By "broad stratified" is meant a similar zone of cells exceeding 0.6 mm. but not exceeding a width of about 2.0 mm. By "bulky" is meant still broader stratified nevi and large nevi of nodular and irregular shapes. The tabulation of results by age and anatomic location is shown in Table I.

It is evident that there are certain relationships between both age and location and the size and shape of nevi. The narrow stratified nevi are

TABLE I
Size and General Configuration of Nevi According to Age and Anatomic Site

	Age group (years)							Total
	0-9	10-19	20-29	30-39	40-49	50-59	60-	
Head and Neck								
Narrow stratified	2	2	0	0	0	0	1	5
Broad stratified	5	2	1	0	2	0	0	10
Bulky	2	6	7	8	6	11	8	48
Trunk								
Narrow stratified	7	2	0	1	1	3	0	14
Broad stratified	1	2	2	0	0	1	2	8
Bulky	2	8	9	6	9	5	6	45
Extremities, proximal								
Narrow stratified	1	0	0	0	0	0	0	1
Broad stratified	1	1	0	0	1	3	0	6
Bulky	0	3	6	4	8	2	1	24
Extremities, distal								
Narrow stratified	5	4	2	5	4	1	0	21
Broad stratified	2	1	3	1	2	0	0	9
Bulky	2	1	2	0	1	3	0	9
Totals								
Narrow stratified	15	8	2	6	5	4	1	41
Broad stratified	9	6	6	1	5	4	2	33
Bulky	6	18	24	18	24	21	15	126
	30	32	32	25	34	29	18	200

most common in the first decade. The proportion of bulky nevi is greater in the second decade and still greater in the third, but thereafter there is little change. This roughly indicates the rate of growth or cellular multiplication of nevi. At all ages the narrow stratified nevi are least common on the head and neck, and most common on the distal parts of the extremities.

Junctional and Intra-epidermal Cellular Proliferation. The cells of a pigmented nevus vary in appearance in the epidermis and corium. By "nevus cell" is meant the characteristic cell of the corium. It is described subsequently. The cells of the epidermis and junctional zone are often designated as the "clear cells." The term is not entirely descriptive because the density, amount, and degree of pigmentation of the cytoplasm vary. Furthermore, there is no clear-cut distinction from nevus cells, for transitions in appearance and direct continuity with nevus cells can be seen. In this paper these cells are spoken of as the intra-epidermal cells or junctional cells of the nevus.

The junctional cells usually appear in round clumps within the epidermis or attached to the deep surface of the epidermis. Clumps of cells separated from the epidermis by collagenous fibrils ("snared off") are designated as subjunctional. Undoubtedly some of the clumps so designated could be demonstrated to connect with the epidermis if serial sections were made. However, for the purposes of comparison and charting it was decided that the term junctional proliferation should be restricted to the cells within the epidermis or joined to it at its deep margin.

Infrequently there is blending of broad bands of cells in the superficial corium with those of the epidermis. These cells are not in clumps and often resemble the deeper nevus cells more closely than the intra-epidermal "clear" cells. This appearance was called junctional proliferation also. However, it is almost invariably associated with the usual type of junctional proliferation and its inclusion does not significantly affect the tabulation.

It was apparent from the start that junctional proliferation is a quantitative consideration. The proliferation was classified as marked, moderate, slight, or none. "Marked" means many foci of proliferation; "moderate," occasional; "slight," sparse; "none," that no such change was found, or, at most, a rare focus of proliferation of a few intra-epidermal cells or junction of a few cells in the epidermis and dermis. In some instances isolated "clear" cells were present in the basal layer of the epidermis. Rarely a few were grouped together. This is often associated with hyperpigmentation of the basal layer, and is not classified as junctional proliferation, because there is no proliferation of clumps or extension of such cells downward from the epidermis. These changes are the same as in lentigo.

The observations of junctional proliferation are applied to hair follicles as well as to the surface epithelium. Proliferation of cells in sweat glands is evident only in the nevi of the first decade. The fact that nevi

in this decade are comparatively acellular permits easy distinction of these foci. However, it is reasonably certain that the diminution in subsequent decades is absolute. The observations are recorded in relation to age and location in Table II and in relation to size and shape of

TABLE II
Junctional Proliferation According to Age and Site

	Age group (years)							Total
	0-9	10-19	20-29	30-39	40-49	50-59	60-	
Head and Neck								
Marked	3	0	0	0	0	0	0	3
Moderate	4	2	0	0	0	1	0	7
Slight	1	3	0	1	0	0	0	5
None	1	5	8	7	8	10	9	48
Trunk								
Marked	5	2	0	0	0	0	0	7
Moderate	4	3	2	0	0	1	0	10
Slight	0	5	3	3	0	1	0	12
None	1	2	6	4	10	7	8	38
Extremities, proximal								
Marked	2	0	0	0	0	0	0	2
Moderate	0	3	1	0	0	0	0	4
Slight	0	1	1	1	0	0	0	3
None	0	0	4	3	9	5	1	22
Extremities, distal								
Marked	8	3	3	3	1	0	0	18
Moderate	1	1	0	2	1	0	0	5
Slight	0	1	1	0	3	1	0	6
None	0	1	3	1	2	3	0	10
Totals								
Marked	18	5	3	3	1	0	0	30
Moderate	9	9	3	2	1	2	0	26
Slight	1	10	5	5	3	2	0	26
None	2	8	21	15	29	25	18	118
	30	32	32	25	34	29	18	200

nevi in Table III. The classification of size and shape is the same as that used in Table I. These tables indicate that there is significant relationship of junctional proliferation with age. The proliferation is most frequent and greatest in the first decade and rapidly diminishes in subsequent age groups.

Because of differences, it is convenient to compare the trends of the nevi of the distal parts of the extremities with those of all other locations, as shown in Table IV. Junctional proliferation in nevi of adults is more frequent when the nevi are located on the distal parts of the extremities. In this site, nonetheless, there is a diminution in degree and frequency with age, and of the 11 nevi so located in patients beyond 40 years of age, only 2 showed it to a moderate or marked degree.

There is no abrupt cessation of junctional proliferation at any age. In Table IV, the first 2 decades are subdivided into 5-year periods. This shows that the diminution in frequency begins before puberty and does not stop abruptly.

TABLE III
Junctional Proliferation According to Age and General Appearance of Nevus

	Age group (years)							Total
	0-9	10-19	20-29	30-39	40-49	50-59	60-	
Narrow stratified nevus								
Marked	11	5	2	3	0	0	0	21
Moderate	4	1	0	1	1	1	0	8
Slight	0	0	0	0	3	0	0	3
None	0	2	0	2	1	3	1	9
Broad stratified nevus								
Marked	4	0	0	0	1	0	0	5
Moderate	3	0	1	1	0	0	0	5
Slight	1	4	1	0	0	0	0	6
None	1	2	4	0	4	4	2	17
Bulky nevus								
Marked	3	0	1	0	0	0	0	4
Moderate	2	8	2	0	0	1	0	13
Slight	0	6	4	5	0	2	0	17
None	1	4	17	13	24	18	15	92
Totals								
Marked	18	5	3	3	1	0	0	30
Moderate	9	9	3	2	1	2	0	26
Slight	1	10	5	5	3	2	0	26
None	2	8	21	15	29	25	18	118
	30	32	32	25	34	29	18	200

Although the nevi of childhood are of the narrow stratified type, it is seen from Table III that junctional proliferation is not confined to this type. Clumps of intra-epidermal cells are often found in bulky nevi.

TABLE IV
Comparison of Junctional Proliferation of Nevi of the Distal Parts of the Extremities with Nevi of All Other Sites

	Age group (years)								
	0-4	5-9	10-14	15-19	20-29	30-39	40-49	50-59	60-
Distal parts of the extremities	100	100	67	No cases	43	83	29	0	No cases
All other sites	86	86	60	25	12	0	0	8	0

The figures express per cent of nevi showing moderate to marked junctional proliferation.

Contrariwise, the presence of a narrow stratified nevus does not necessarily indicate a nevus of childhood or a nevus with junctional proliferation. Some nevi never do become bulky but nevertheless follow the same trend of diminished junctional proliferation with advancing years.

The exceptions to the trend are discussed later. These include the nevi

of adults which have scanty nevus cells but much junctional proliferation and thereby resemble the nevi of childhood, and the infrequent cases in which nevi of childhood lack junctional proliferation.

Mitotic Figures. Mitotic figures are rare in pigmented nevi. Miescher⁸ commented that they are exceptionally infrequent in the intra-epidermal nests and may be entirely absent. The rarity was borne out by the present investigation.

In sections from the entire series, mitotic figures were identified in only 13 nevi. In 2, there were 2 mitotic figures in each. In 1, there were 5 mitotic figures. Six of the patients were in the first decade of life, 4 in the second, 2 in the third, and 1 in the fifth. In 7 cases there was moderate or marked proliferation in the epidermis or at the dermo-epidermal junction; in 2 there was slight, and in 4 no proliferation. Of the 19 mitotic figures, 5 occurred in the intra-epidermal, junctional, or immediately subjunctional cells. The remainder were in the nevus cells. They were not seen in nevus cells of the fusiform and fibrillar type. Exceptional note is made of a small nevus, said to be of over 10 years' duration, from the dorsum of the hand of a 42-year-old man. It lacked junctional cells and pigmented cells. Five mitotic figures were counted, scattered at random among the nevus cells. There has been no recurrence of this lesion 10 years after removal.

Distribution of Nevus Cells. In all cases there were nevus cells in the upper part of the corium. There was a tendency for the cells of nevi of the trunk to be closer to the epidermis than the cells of nevi of the head and neck, which tended to have a definite (although thin and focally interrupted) zone of collagenous connective tissue just beneath the epidermis.

The number of nevi with cells in the mid-corium and deep corium are shown in Table V, correlated with age and site. The nevi were classified as to the presence of none, few, or many nevus cells in the corium deep to the uppermost two or three bands of coarse collagenous tissue. This is the collagenous stratum which can be traced laterally to the adjacent normal corium, and not the finer fibrils intermingled with nevus cells.

Nevus cells were present in the deep parts of the corium in about the same proportion of nevi in all age groups. However, it is true that in older life the mass of the deep cells was greater than in the first decade as was also the mass of the superficial cells. This has not been analyzed statistically but was readily apparent in the histologic material. The largest proportion of nevi with deeply situated cells were of the head and neck. Nevi of the proximal part of the extremities, trunk, and distal part

of the extremities showed a progressively smaller proportion in the order stated.

The nevi with cells deep in the corium were further analyzed as to their relationship to hair follicles and sweat glands. Observations con-

TABLE V
Nevi Showing Cells in Deeper Part of Corium

	Age group (years)							Total
	0-9	10-19	20-29	30-39	40-49	50-59	60-	
Head and neck								
None	0	0	0	0	1	0	0	1
Few	2	2	1	1	1	0	2	9
Many	7	7	7	7	6	8	6	48
Inadequate biopsy	0	1	0	0	0	3	1	5
Trunk								
None	3	4	0	3	1	3	3	17
Few	3	2	8	1	6	4	3	27
Many	3	6	3	1	2	2	0	17
Inadequate biopsy	1	0	0	2	1	0	2	6
Extremities, proximal								
None	0	0	0	0	0	2	0	2
Few	1	3	6	2	3	1	1	17
Many	1	1	0	2	6	2	0	12
Inadequate biopsy	0	0	0	0	0	0	0	0
Extremities, distal								
None	1	4	1	4	3	2	0	15
Few	4	0	3	1	3	1	0	12
Many	3	2	3	1	1	1	0	11
Inadequate biopsy	1	0	0	0	0	0	0	1
Totals								
None	4	8	1	7	5	7	3	35
Few	10	7	18	5	13	6	6	65
Many	14	16	13	11	15	13	6	88
Inadequate biopsy	2	1	0	2	1	3	3	12
	30	32	32	25	34	29	18	200

cerning this were noted by Unna,^{1,2} Masson,¹⁴ and others. The deep nevus cells were classified as: perifollicular, if all the cells formed a distinct aggregation about hair follicles and sweat glands; perifollicular and scattered, if aggregates about follicles and sweat glands were accompanied by a more diffuse distribution; scattered, if there was no distinct grouping. The results are presented in Table VI which shows that in a majority of nevi the deep cells tend to have a perifollicular pattern. Even if some of the cells appear diffusely scattered between follicles there is usually a perceptible aggregation about these structures. The perifollicular arrangement is most striking in the nevi of children, in which case the mass of cells is not bulky. It is least conspicuous in the nevi of the head and neck, especially in adult life, and is progressively

more noticeable in the proximal parts of the extremities, the trunk, and the distal parts of the extremities. The paradoxical lack of distinct perifollicular grouping in nevi of the head and neck in adults is difficult to explain but it may be related to the profusion of follicles and sweat glands causing a confluence of aggregates.

TABLE VI
Distribution of the Cells in the Deep Corium

	Age group (years)							Total
	0-9	10-19	20-29	30-39	40-49	50-59	60-	
Head and Neck								
Perifollicular	3	2	0	0	0	0	0	5
Scattered	4	4	7	3	4	5	5	32
Perifollicular and scattered	2	3	1	5	3	3	3	20
Inadequate biopsy	0	1	0	0	0	3	1	5
Trunk								
Perifollicular	3	1	6	1	3	3	1	18
Scattered	1	3	2	1	3	0	2	12
Perifollicular and scattered	2	4	3	0	2	3	0	14
Inadequate biopsy	1	0	0	2	1	0	2	6
Extremities, proximal								
Perifollicular	1	3	4	1	1	1	1	12
Scattered	0	0	0	1	3	1	0	5
Perifollicular and scattered	1	1	2	2	5	1	0	12
Inadequate biopsy	0	0	0	0	0	0	0	0
Extremities, distal								
Perifollicular	5	0	5	1	2	0	0	13
Scattered	1	0	0	0	2	1	0	4
Perifollicular and scattered	1	2	1	1	0	1	0	6
Inadequate biopsy	1	0	0	0	0	0	0	1
Totals								
Perifollicular	12	6	15	3	6	4	2	48
Scattered	6	7	9	5	12	7	7	53
Perifollicular and scattered	6	10	7	8	10	8	3	52
Inadequate biopsy	2	1	0	2	1	3	3	12
	26	24	31	18	29	22	15	165

In general, deep nevus cells are found among and around the follicular epithelial cells and among and around the cells of sweat glands. This in itself does not prove an epithelial origin, for nerve fibrils and terminations are also abundant in these distributions.

Occasionally there are nevus cells among the fibers of the arrectores pilorum muscles. This may appear to refute the epithelial theory of origin but this in turn is not conclusive for the muscle is intimately related with the follicle anatomically and embryologically.

Enclosure of small vascular channels and small nerves occurs especially in the large nevi of adult life. It is not constant in random sections and does not in itself substantiate a theory of either perivascular or perineural origin of nevus cells.

Nevus cells occasionally extend as deeply as the subcutaneous fat. Infiltration among fat cells is most frequent in nevi of the head. In nevi which overlie skeletal muscle, as in those of the lip or eyelid, penetration to and around some of the superficial skeletal muscle fibers may take place. This is not to be interpreted as invasion (Fig. 8).

In summary, the superficial cells of a nevus proliferate in a zone lying parallel to the surface and in their growth tend to separate the coarsely fibrous part of the corium from the epidermis. The deep cells of a nevus tend to be distributed in and about follicles and sweat glands, although diffusely scattered cells are seen also.

Fibrillar and Nerve-like Elements. There are transitional appearances between the intra-epidermal "clear" cells and the nevus cells of the corium. The latter in turn undergo progressive changes. In the more superficial corium, especially in nevi of youth, the nevus cells may be exactly the same as the cells at the dermo-epidermal junction. A little more deeply the cells are usually somewhat smaller, usually pigment-free, but retain a large nucleus and nucleolus. Still more deeply, as a rule, the cells are smaller, nuclei are more compact, and pigment is almost always absent. Cells with nucleoli are not so abundant here as in the superficial corium. Occasionally a central pale round spot is seen in the nucleus, larger than a nucleolus and occasionally having a faint brown color. The nevus cells may be spread in large masses, or in groups surrounded by fibrils. There is gradual transition to cells of oval or fusiform type. Definition of cytoplasmic borders is lost and nuclei are adjacent to or enclosed by faintly eosinophilic fibrils, which usually run in the same axis as that of the nucleus and are sometimes arranged as ribbon-like fasciculi. These are usually seen in the lowermost part of the mass of nevus cells but may be both deep and superficial, especially in the nevi of older people. In some the fibrils are abundant and compact and often have a resemblance to Wagner-Meissner corpuscles. In the more fibrillar nevi nuclei are in many instances irregular in shape, densely stained, and often clumped. In the fibrillar parts of a nevus there are comparatively few nuclei. It is not possible to state from this study how much of this is relative, in view of the great increase of fibrils, but an absolute decrease is favored.

That the above transition in the appearance of nevus cells is developmental is shown by correlation of fibrillar elements with age. The presence of fibrils is quantitative. The degree of occurrence was classified as absent or slight, moderate, and marked. The degrees are arbitrary and difficult to define. By absent or slight is meant that none or only a few cells were associated with fibrils. By marked is meant that extensive

areas in the microscopic section were made up of fibrillar cells. Often the areas were comparatively anuclear, composed almost entirely of fibrils alone. Moderate is an intermediate appearance; the fibrillar cells were not predominant nor did they occupy large foci. The results are shown in Table VII.

TABLE VII
The Presence of Fibrillar Elements in Nevi

	Age group (years)							Total
	0-9	10-19	20-29	30-39	40-49	50-59	60-	
Head and Neck								
None or few	4	4	0	1	0	0	0	9
Moderate number	2	5	4	2	1	0	0	14
Many	3	1	4	5	7	11	9	40
Trunk								
None or few	9	2	2	1	0	1	0	15
Moderate number	1	5	4	0	3	3	1	17
Many	0	5	5	6	7	5	6	34
Inadequate biopsy	0	0	0	0	0	0	1	1
Extremities, proximal								
None or few	1	1	0	0	0	0	0	2
Moderate number	1	2	2	1	1	1	1	9
Many	0	1	4	3	8	4	0	20
Extremities, distal								
None or few	5	4	3	4	2	0	0	18
Moderate number	4	1	3	1	3	1	0	13
Many	0	1	1	1	2	3	0	8
Totals								
None or few	19	11	5	6	2	1	0	44
Moderate number	8	13	13	4	8	5	2	53
Many	3	8	14	15	24	23	15	102
Inadequate biopsy	0	0	0	0	0	0	1	1
	30	32	32	25	34	29	18	200

A further segregation of nevi was made in which the nevi with foci which resembled neurofibrillar tissue were selected. Here again, criteria of selection cannot be sharply defined. It is based on the presence of readily recognized foci of delicate fibrillar tissue. Usually this is arranged in delineated ribbons and nests. In many, there are structures resembling Wagner-Meissner corpuscles. Thus the cylindroid, ribbon-like, and plate-like structures described by Masson¹⁴ are all included. The results are shown in Table VIII.

It is evident that there is a progressive increase of fibrils and what resembles neurofibrillar tissue with increasing age, and that such tissue is the final phase of differentiation of the nevus cells. Broders and Fletcher,²⁰ in the interpretation of a nevus which had undifferentiated cells superficially and resembled neurofibrillar tissue deeply, came to

the same conclusion. Interpretation of the fibrillar tissue or structures resembling tactile corpuscles as the source of the nevus cells is not justifiable.

It is thought, in agreement with the interpretations of others, notably

TABLE VIII
The Presence of Nerve-like Elements

	Age group (years)							Total
	0-9	10-19	20-29	30-39	40-49	50-59	60-	
Head and neck								
None	9	10	8	5	4	3	2	41
Present	0	0	0	3	4	8	7	22
Trunk								
None	10	12	9	5	6	8	4	54
Present	0	0	2	2	4	1	2	11
Inadequate biopsy	0	0	0	0	0	0	2	2
Extremities, proximal								
None	6	3	6	4	7	2	1	29
Present	0	1	0	0	2	3	0	6
Extremities, distal								
None	5	6	6	6	7	2	0	32
Present	0	0	1	0	0	2	0	3
Totals								
None	30	31	29	20	24	15	7	156
Present	0	1	3	5	10	14	9	42
Inadequate biopsy	0	0	0	0	0	0	2	2
	30	32	32	25	34	29	18	200

Kromayer²¹ and Masson,¹⁴ that the fibrils arise from the nevus cells and are not a reactive fibrosis.

In general, nevi in which fibrils are abundant are not associated with much junctional proliferation, but there are exceptions; for example, the instance recorded in the second decade (actually 12 years of age) and one instance in the third decade. In one nevus in a 7-months-old child, located on the back and not part of this series of 200, there was marked junctional proliferation but the major part of the nevus, extending from the upper cutis into the subcutaneous fat, consisted of fibrillar cells.

Pigmentation. The degree of pigmentation was arbitrarily and roughly expressed as none, 1 plus, 2 plus, 3 plus, and 4 plus. Pigmentation of the basal epidermis was not included even though it was intense in some instances and resembled the changes of lentigo. On the other hand, pigment in chromatophores among the nevus cells was included. The results in Table IX show the trend as to age and anatomic site. This

indicates that pigmentation tends to diminish with age. Furthermore, it tends to be least intense in nevi of the head and neck. The latter observation may be correlated with the additional observation that pigment is largely related to nevus cells lying in a stratum just beneath the epidermis and is not common in nevus cells around the follicles and

TABLE IX
Pigmentation According to Age and Site

	Age group (years)							Total
	0-9	10-19	20-29	30-39	40-49	50-59	60-	
Head and neck								
None	1	0	0	3	2	4	3	13
One plus	3	4	5	5	3	4	3	27
Two plus	2	6	2	0	3	2	0	15
Three plus	1	0	1	0	0	0	0	2
Four plus	2	0	0	0	0	1	3	6
Trunk								
None	0	0	0	1	3	1	3	8
One plus	1	1	3	3	5	5	4	22
Two plus	4	6	4	1	2	3	1	21
Three plus	4	3	4	2	0	0	0	13
Four plus	1	2	0	0	0	0	0	3
Extremities, proximal								
None	0	0	0	1	2	3	1	7
One plus	0	0	2	2	3	1	0	8
Two plus	0	2	4	1	4	0	0	11
Three plus	2	0	0	0	0	1	0	3
Four plus	0	2	0	0	0	0	0	2
Extremities, distal								
None	0	0	0	1	1	1	0	3
One plus	1	1	3	2	1	1	0	9
Two plus	0	2	3	2	1	2	0	10
Three plus	7	3	1	1	4	0	0	16
Four plus	1	0	0	0	0	0	0	1
Totals								
None	1	0	0	6	8	9	7	31
One plus	5	6	13	12	12	11	7	66
Two plus	6	16	13	4	10	7	1	57
Three plus	14	6	6	3	4	1	0	34
Four plus	4	4	0	0	0	1	3	12
	30	32	32	25	34	29	18	200

sweat glands or diffusely scattered in the deeper corium. Even in the nevi of childhood in which intra-epidermal clumps of "clear" cells are seen along follicles and sweat glands, pigment is scanty or absent in these locations. The nevi of the face and neck, as previously noted, contain relatively more of the deeply placed diffuse and perifollicular cells.

The age distribution of pigmentation suggests a relationship to junctional proliferation, and this is borne out in the correlation of pigmentation and junctional proliferation, as shown in Table X.

The cells at the dermo-epidermal junction and of the upper part of the corium tend to be the most intensely pigmented and hence there is a rough correlation with proliferation at the dermo-epidermal junction. As pointed out, the junctional and subjunctional cells are scanty or absent in older age groups. The presence of chromatophores, usually in

TABLE X
Relationship of Pigmentation and Junctional Proliferation

	Age group (years)							Total
	0-9	10-19	20-29	30-39	40-49	50-59	60-	
No junctional proliferation								
No pigment	0	0	0	6	8	9	7	30
One plus	2	4	11	7	11	11	7	53
Two plus	0	3	7	1	9	3	1	24
Three plus	0	1	3	1	1	1	0	7
Four plus	0	0	0	0	0	1	3	4
Slight junctional proliferation								
No pigment	0	0	0	0	0	0	0	0
One plus	1	2	1	3	0	0	0	7
Two plus	0	6	3	1	1	2	0	13
Three plus	0	1	1	1	2	0	0	5
Four plus	0	1	0	0	0	0	0	1
Moderate junctional proliferation								
No pigment	0	0	0	0	0	0	0	0
One plus	1	0	0	2	1	0	0	4
Two plus	3	5	1	0	0	2	0	11
Three plus	3	1	2	0	0	0	0	6
Four plus	2	3	0	0	0	0	0	5
Marked junctional proliferation								
No pigment	1	0	0	0	0	0	0	1
One plus	1	0	1	0	0	0	0	2
Two plus	3	2	2	2	0	0	0	9
Three plus	11	3	0	1	1	0	0	16
Four plus	2	0	0	0	0	0	0	2
Totals								
No pigment	1	0	0	6	8	9	7	31
One plus	5	6	13	12	12	11	7	66
Two plus	6	16	13	4	10	7	1	57
Three plus	14	6	6	3	4	1	0	34
Four plus	4	4	0	0	0	1	3	12
	30	32	32	25	34	29	18	200

the superficial part of the nevus, suggests that pigment is discharged from cells but actual death and phagocytosis of pigmented nevus cells would produce the same effect. Whether the deeper cells have lost, or never had, the property of pigment production in these sites cannot be answered from the above observations.

Multinucleated Cells. Multinucleated cells are common in nevi. Occasionally their presence or absence is carefully noted in the differentia-

tion of a nevus from melanoblastoma (Becker,²² Dawson²³), but the reader does not gain a clear idea of their special significance and is left with the impression that they indicate melanoblastoma. Spitz,¹⁹ however, stressed the importance of the presence of giant cells in "juvenile melanoma," which distinguished them from "adult melanoma" in about half the cases.

It was found that multinucleated cells are of two types. The first appears as a comparatively small cluster of nuclei. In some instances these appear to lie in a common cytoplasm. In others this is not certain and the multinucleated cell may actually be an aggregate of cells, distinguished from other aggregates only by the small circular pattern of the nuclear cluster. Frequently the nuclei are densely stained, vacuolated, or distorted, appearing in curved or irregular shapes. A multinucleated cell of the second type is large and the cytoplasm is distinct. Usually the nuclei are in a peripheral ring but may be arranged in central clusters. Nuclei are not pyknotic. The chromatin pattern is delicate and sometimes there is a nucleolus. These giant cells are usually in the superficial part of the nevus.

The occurrence of multinucleated cells of both types, according to age and location, is seen in Table XI. There is no significant change in the

TABLE XI
Giant Cells of Both Kinds

	Age group (years)							Total
	0-9	10-19	20-29	30-39	40-49	50-59	60-	
Head and neck								
None	4	6	1	2	5	4	4	26
Scarce	1	2	1	2	2	1	2	11
Many	4	2	6	4	1	6	3	26
Trunk								
None	13	6	3	5	6	6	3	42
Scarce	0	4	7	1	3	2	4	21
Many	1	2	1	1	1	1	1	8
Extremities, proximal								
None	2	2	3	3	3	3	1	17
Scarce	0	1	2	0	4	1	0	8
Many	0	1	1	1	2	1	0	6
Extremities, distal								
None	3	5	4	6	6	1	0	25
Scarce	2	1	2	0	1	3	0	9
Many	0	0	1	0	0	0	0	1
Totals								
None	22	19	11	16	20	14	8	110
Scarce	3	8	12	3	10	7	6	49
Many	5	5	9	6	4	8	4	41
	30	32	32	25	34	29	18	200

incidence throughout life. They are most abundant in nevi of the head and neck, and least in the nevi of the distal parts of the extremities.

The occurrence of multinucleated cells of the second type, according to age and location, is seen in Table XII. Here again, there is no sig-

TABLE XII
Large Giant Cells

	Age group (years)							Total
	0-9	10-19	20-29	30-39	40-49	50-59	60-	
Head and neck								
None	7	8	5	7	6	9	8	50
Scarce	1	1	2	1	2	1	0	8
Many	1	1	1	0	0	1	1	5
Trunk								
None	14	8	7	5	8	9	8	59
Scarce	0	3	4	2	1	0	0	10
Many	0	1	0	0	1	0	0	2
Extremities, proximal								
None	2	3	5	4	5	4	1	24
Scarce	0	0	1	0	3	0	0	4
Many	0	1	0	0	1	1	0	3
Extremities, distal								
None	4	5	6	6	7	4	0	32
Scarce	1	1	1	0	0	0	0	3
Many	0	0	0	0	0	0	0	0
Totals								
None	27	24	23	22	26	26	17	165
Scarce	2	5	8	3	6	1	0	25
Many	1	3	1	0	2	2	1	10
	30	32	32	25	34	29	18	200

nificant change throughout life. The cells are least common in nevi of the distal parts of the extremities and most common in nevi of the head and neck, and proximal parts of the extremities. It is to be expected that giant cells of both types would be less numerous in nevi of the distal parts of the extremities because these are usually "narrow stratified" nevi and cells of all types are fewer in them than in the bulky nevi of other sites.

Inflammation. The nevi were studied as to the degree of inflammation present in and around each of them. This was arbitrarily subdivided as none or questionable, slight, moderate, and marked. Almost every inflammatory lesion was of chronic or subacute nature. In 4 cases the inflammation was acute exudative. In 2 of these there was ulceration. For simplification, all types are grouped and differentiated only as to degree. The results are shown in Table XIII.

It is seen that inflammation is more common in the older age groups

and is infrequent in the first decade. There is therefore no parallelism between inflammation and active (benign) proliferation of a nevus. Inflammation was more frequent and more active in the larger nevi and especially in those with large hair follicles. The follicles in nevi are often

TABLE XIII
Inflammation

	Age group (years)							Total
	0-9	10-19	20-29	30-39	40-49	50-59	60-	
Head and neck								
None	8	4	3	3	3	1	2	24
Slight	0	2	3	3	4	5	3	20
Moderate	1	4	2	2	1	4	4	18
Marked	0	0	0	0	0	1	0	1
Trunk								
None	10	4	5	5	5	6	2	37
Slight	0	6	5	2	4	3	4	24
Moderate	0	0	1	0	0	0	2	3
Marked	0	2	0	0	1	0	0	3
Extremities, proximal								
None	2	4	4	0	5	4	1	20
Slight	0	0	1	4	2	1	0	8
Moderate	0	0	0	0	2	0	0	2
Marked	0	0	1	0	0	0	0	1
Extremities, distal								
None	8	5	3	6	5	2	0	29
Slight	0	1	3	0	2	1	0	7
Moderate	1	0	1	0	0	0	0	2
Marked	0	0	0	0	0	1	0	1
Totals								
None	28	17	15	14	18	13	5	110
Slight	0	9	12	9	12	10	7	59
Moderate	2	4	4	2	3	4	6	25
Marked	0	2	1	0	1	2	0	6
	30	32	32	25	34	29	18	200

dilated and filled with keratin débris. There is associated with this in many instances a perifollicular or intrafollicular leukocytic infiltration and exudation. The cells are principally lymphocytes but occasionally eosinophils and neutrophils are present. Occasionally there are foreign body giant cells. Infiltration of lymphocytes, not associated with follicles, is usually most noticeable at the lateral margins of nevi close to the surface of the normal skin. Less frequently, it is at the deep margin. It is difficult to detect slight degrees of lymphocytic infiltration or fibroblastic proliferation, for they are often closely imitated by the nevus cells. Next to lymphocytes, eosinophils were the most common form of leukocyte.

Inflammation may occur in any site. The greatest frequency is in nevi of the head and neck, evidently because of the large number of hair

follicles present. It is least common in nevi of the extremities, especially of the distal parts. This is partly explained by the large percentage of hairless nevi of the distal extremities and by the preponderance of flat ("narrow stratified") nevi which are less subject to trauma. These observations are contrary to widespread beliefs.

Inflammation has been stressed as an important sign of melanoblastoma (Miescher⁸), but from the above it is evident that many other factors must be considered. However, its presence in a flat hairless nevus is more significant than in a large nevus with numerous hair follicles.

Vascular Changes. In large nevi, especially of adult life, and nevi which tend to be pedunculated, dilatation of capillaries, venules, and lymphatics is conspicuous. In addition, interstitial edema is noted occasionally. Often the nevus cells are spread apart and lacunae suggest acini or channels. Rarely the faintly staining fluid precipitates in these spaces. Usually the above changes occur in nevi which are at least partly fibrillar. Unna's^{1,2} concept that the atrophy of nevus cells and fibril formation ("molluscoid" changes) are directly related to constriction at the base and lymph edema is to be considered. However, fibrillar changes in flat nevi and nonpedunculated nevi with or without vascular dilatation are hardly compatible with this theory. Yet, that trophic disturbance may account for the later changes in nevi cannot be denied.

Miscellaneous Observations. Focal ossification in the subcutaneous fat was noted in 2 cases, and focal calcification of the subcutaneous fat in one case.

One nevus of the back of a 10-year-old child had been treated by irradiation. Because of subsequent dermatitis and ulceration the lesion was excised widely. The nevus was benign histologically but the dermatitis was complicated by squamous cell carcinoma. The case was followed for 18 years without recurrence or metastasis.

In the first part of this investigation certain features of nevi were analyzed as they relate to age and anatomic site. In order to facilitate further discussion, a summary of certain trends is advantageous.

Four features were greatly influenced by age: junctional and intra-epidermal cellular proliferation, mitotic figures, size (or total cellularity), and differentiation of nevus cells to fibrillar forms. In order to simplify further discussion, the nevi have been re-evaluated and segregated into five types, determined by the above features with the exception of the presence of mitotic figures. The types are labelled A, B, C, D, and E. The characteristics of these types are:

A. The nevus consists mostly of intra-epidermal cells and cells at the dermo-epidermal junction. This includes, of course, intra-epidermal cells along hair follicles and sweat glands. There are few nevus cells in the corium.

B. The nevus consists of intra-epidermal cells and cells at the dermo-epidermal junction and there are nevus cells in fair number in the corium.

C. The nevus consists mostly of nevus cells in the corium but there is still moderate to marked cellular proliferation in the epidermis or at the dermo-epidermal junction.

D. The nevus consists of nevus cells and there is no, or very little, junctional proliferation.

E. This corresponds to type D except that many of the nevus cells are fibrillar in type.

The general trend in regard to the appearance of nevi at different ages is summarized in Table XIV. It is seen that there is a definite trend from the A type to the E type and that the age of the patient can be correlated roughly with the structure of the nevus. However, there are exceptions and these will be discussed subsequently.

TABLE XIV
Distribution of Nevi as to Type at Different Ages

Age group (years)	Type of nevus					Total
	A	B	C	D	E	
0-4	3	6	3	1	0	13
5-9	3	8	4	2	0	17
10-14	2	2	6	6	0	16
15-19	0	1	2	10	3	16
20-29	1	1	3	13	14	32
30-39	1	2	2	6	14	25
40-49	0	0	2	8	24	34
50-59	0	0	2	6	21	29
60-	0	0	0	2	16	18
Totals	10	20	24	54	92	200

Appearance of Multiple Nevi. In those instances in which multiple nevi from the same patient were removed at the same time the microscopic appearance was practically identical. These are analyzed in Table XV. In only one case was there notable variation, in which instance one nevus was of type A and one of type D.

Duration of Nevi. Data concerning the patients' ideas of the duration of the nevi were obtained in 87.5 per cent of the cases. Of these, 157 nevi or 89.7 per cent were stated to have been present since birth or childhood, or, in adults, for an indefinitely long period of time. Hence the trend noted above correlates with the duration of the nevus as well as with the age of the patient.

In 18 instances the nevi were stated to be of significantly shorter duration than the age of the patients. These are analyzed in Table XVI.

It may be suspected from the trend described that nevi of shorter duration in adults should resemble the nevi of childhood. However,

TABLE XV
Cases of Multiple Nevi Analyzed According to Type

	Age group (years)						
	0-9	10-19	20-29	30-39	40-49	50-59	60-
Number	3	1	1	3	4	1	1
Combination of types	CAA BB DD	ED	DA	AC EE CB	EE EE ED DC	EE	EE

this conclusion is not substantiated. Most of these nevi correspond in type to those which date from birth or childhood. In many instances the histories are questionable. It does not seem right that a large nevus composed often of fibrillar cells should be present only a matter of

TABLE XVI
Analysis of Nevi Stated to Be of Significantly Shorter Duration than Age of Patient

Case no.	Type of nevus	Age	Location	Reason removed	Stated duration	Recent growth	Follow-up
32	D	18	Behind ear	Growth	2-3 mos.	Yes	7 yrs.
64	D	23	Nose	Unknown	6 mos.	Yes	4 yrs.
70	E	29	Behind ear	Annoying when put glasses on	10 yrs.	Yes	2 yrs.
80	D	27	Breast	Incidental	2 yrs.	Yes	4 yrs.
81	E	27	Perineum	Incidental	6 mos.	No	9 yrs.
97	E	33	Scalp	Interfered with combing of hair	Months	Yes	4 yrs.
98	E	33	Scalp	Interfered with combing of hair	Months	Yes	4 yrs.
105	E	34	Back	Incidental	8 yrs.	None in last 3 yrs.	4 yrs.
115	A	37	Sole	Incidental	1 yr.	Yes*	1 yr.
119	B	36	Sole	Recent appearance	Few days	Yes	1 yr.
126	E	43	Chin	Incidental	4 or 5 yrs.	Yes	3 yrs.
149	D	41	Toe	Irritation	10 yrs.	Yes	6 yrs.
150	C	41	Toe	Irritation	10 yrs.	Yes	6 yrs.
176	E	56	Shoulder	Incidental	2 yrs.	No	12 yrs.
184	E	74	Neck	Growth	6 yrs.	Yes	5 yrs.
185	E	61	Canal of ear	Growth and pain	15 yrs.	Yes	5 yrs.
186	E	65	Face	Growth	1 yr.	Yes	5 yrs.
187	E	60	Eyelid	Growth	5 yrs.	Yes	13 yrs.

* Classed as recent growth because of recent appearance.

months or a few years, as was stated in some instances. It may be, as is the case in nevi of the scalp, back, auditory canal, behind the ear, or on the perineum, that the patients were not aware of the presence of the nevi for the greater part of their lives. Furthermore, since some were removed incidental to other surgical procedures, the patient may not

have been aware of the nevus at any time. The 3 nevi more in keeping with those of childhood (types A, B, and C) were of the feet.

Clinical Symptoms in Relation to Location of Nevus and Type of Nevus. The major clinical manifestations were grouped under the following headings: growth, irritation, incidental, and other manifestations. Historical details in the records usually were scanty and interview with the patient often added little information. In most instances the rate of growth was not specified or was poorly described. It was decided that the major classification should be based on the reason for removal of the nevus. Thus, if accelerated growth were the reason for removal it may be accepted that the growth was recent and appreciable. Recent appearance amnestically is considered evidence of recent growth. By irritation is meant soreness, ulceration, or bleeding. By incidental manifestations are meant such circumstances as removal in the course of other surgical procedures, for cosmetic reasons, or as a precautionary measure to avoid melanoblastoma, or because of location. Some nevi of the feet were removed for no other reason than location. In the group called "other manifestations" there was a variety of reasons, including x-ray dermatitis from previous efforts to destroy the nevus, removal in order to fit on glasses, shoe, or football helmet, and interference with combing the hair.

The reasons for removal were subdivided and compared with age and anatomic site, as shown in Table XVII.

Nevi of childhood were removed more frequently because of growth than nevi of adults. Nevi of the distal parts of the extremities were removed because of growth more often than nevi elsewhere. Nevi of the head and neck were next in this regard. The greatest single category in all anatomic sites is incidental removal. However, this accounts for the great majority of those of the trunk and proximal parts of the extremities but for less than one-half of those of the head and distal parts of the extremities. The frequent incidental removal of nevi during abdominal and perineal operations and during delivery accounts for this. Irritation is about equally important as a complaint in regard to all anatomic sites. It is a common complaint in youth as concerns nevi of the trunk but not so in middle and old age. It is a frequent complaint in reference to nevi of the head and neck in adult life and old age, but this is not true of these nevi in youth.

The histologic appearance of the nevus was compared with the major complaint and other symptoms as shown in Table XVIII.

From the totals of all ages it is construed that growth is characteristic of nevi in types A, B, and C. There is alleged growth in other types

TABLE XVII
Reasons for Removal of Nevus as Related to Site and Age

	Age group (years)							Total
	0-9	10-19	20-29	30-39	40-49	50-59	60-	
Head and neck								
Growth	5	2	1	0	0	5	5	18
Irritation	1	0	0	2	1	1	1	6
Incidental	3	7	3	2	6	5	2	28
Other	0	0	0	2	1	0	1	4
Unknown	0	1	4	2	0	0	0	7
Trunk								
Growth	4	0	0	1	2	0	0	7
Irritation	3	4	2	0	0	0	1	10
Incidental	3	7	8	6	8	9	5	46
Other	0	1	0	0	0	0	0	1
Unknown	0	0	1	0	0	0	2	3
Extremities, proximal								
Growth	1	1	1	0	0	0	0	3
Irritation	0	1	0	1	4	0	0	6
Incidental	0	2	5	3	5	5	1	21
Other	1	0	0	0	0	0	0	1
Unknown	0	0	0	0	0	0	0	0
Extremities, distal								
Growth	6	0	0	2	1	2	0	11
Irritation	1	2	1	0	3	0	0	7
Incidental	2	4	3	3	3	2	0	17
Other	0	0	0	0	0	0	0	0
Unknown	0	0	3	1	0	0	0	4
	30	32	32	25	34	29	18	200

TABLE XVIII
Clinical Features as Related to Type of Nevus (Total for All Ages)

Reason removed	Other features	Type of nevus				
		A	B	C	D	E
Growth 39	None 36	2	11	6	4	13
	Irritation 2	0	0	0	1	1
	Other 1	0	0	0	0	1
Irritation 29	None 22	2	1	4	7	8
	Growth 7	1	1	1	2	2
Incidental 112	None 86	2	6	12	24	42
	Growth 11	1	1	0	4	5
	Growth and irritation 2	0	0	0	2	0
	Irritation 2	0	0	0	0	2
Other 6	Unknown 11	0	0	0	3	8
	None 3	1	0	0	0	2
	Growth 2	0	0	0	0	2
Unknown 14	Unknown 1	0	0	0	1	0
	Growth 13	1	0	1	5	6
Totals 200	200	10	20	24	54	92

(D and E) but less often. However, types A, B, and C are characteristic of the first decade in which the common feature is growth. Further analysis of the symptoms as they relate to each age period demonstrates that in any one decade the nevi, no matter what the complaint, are very much alike. The charting of this analysis is lengthy and is not included in this paper.

Nevi of the E type are comparatively acellular and it is reasonable to assume that growth relates to fibrillar proliferation.

Nevi Which Deviate Histologically from the Trend. Certain deviations from the trend were mentioned earlier in this analysis and they are readily seen in Table XIV. These deviations are of two types: (I) those occurring in children but resembling nevi of adults (types D and E), and (II) those occurring in adults but resembling those usual in childhood (types A, B, and C). These are analyzed in Table XIX.

No special conclusion can be drawn concerning the first group. Either certain nevi "mature" more rapidly than usual and proliferation at the dermo-epidermal junction ceases early or the growth of nevus cells is entirely from deep sites. Serial sections would probably be enlightening in these cases, but these were not made.

The second group is of more clinical interest. The first 5 cases are in the second decade and are not striking deviations from the trend. From them, however, it is evident that nevi of types A and B may have a duration of at least a decade. All of these nevi date from birth. It is to be noted that nevi of the feet or hands are represented in 3 of these 5 cases. There are 2 cases of type A nevi in adult life. One, from the foot, was stated to be of 1 year's duration. No history was available in the other, which was from the hand. There were 3 type B nevi in adults, of which one was stated to be present since birth, one for 15 years, and one had been noted only a few days. All were present on the feet. The type C group in adults is more variable in location. Four were from toes, 1 from axilla, 1 from abdomen, 1 from elbow, 1 from cheek and 1 from back. All are said to have been present since birth or childhood, or for a long period of time.

In an analysis of age groups beyond 20 years, it is found that the frequency of active growth in nevi which deviate from the trend is greater than the average for all other nevi of adults. In the group which deviates from the trend, 5 of 12 cases in which information was available, or 42 per cent, listed this feature. This is to be compared with 32 of 104, or 31 per cent, in other nevi of adults. These differences are not statistically significant.

The series is too small for conclusions and study of a larger group is

TABLE XIX
Nevi Which Histologically Deviate from Trend

Case no.	Type of nevus	Age	Location	Reason for removal	Stated duration	Recent growth	Follow-up
<i>Group I</i>							
3	D	3	Forehead	Growth	Since birth	Yes	10 yrs.
6	E	9	Neck	Irritation	Since birth	No	1 yr.
17	E	9	Back	Growth	Since birth	Yes	1 yr.
36	E	16	Face	Cosmetic	As long as can remember	No	2 yrs.
44	E	17	Back	Incidental	Unknown	Unknown	Unknown
45	E	17	Back	Irritation	As long as can remember	No	13 yrs.
<i>Group II</i>							
42	B	17	Pubic region	Incidental	Since birth	No	11 yrs.
46	B	10	Abdomen	Incidental	Since birth	No	12 yrs.
59	B	13	3rd toe	Incidental	Since birth	No	19 yrs.
61	A	12	Foot	Incidental	Since birth	No	1 yr.
62	A	12	Palm	Exposed to trauma	Since birth	Yes	6 mos.
67	A	25	Hand	Unknown	Unknown	Unknown	Unknown
92	B	29	5th toe	Irritation	15 yrs.	No	5 yrs.
72	C	24	Axilla	Irritation	Since birth	No	5 yrs.
78	C	27	Abdomen	Incidental	Since birth	No	8 yrs.
93	C	27	Elbow	Unknown	Since birth	No	8 yrs.
115	A	37	Sole	Incidental	1 yr.	Yes*	1 yr.
116	C	37	Toe	Incidental	Since childhood	No	1 yr.
117	C	30	Toe	Growth	Since birth	Yes	2 yrs.
118	B	30	Toe	Incidental	Since birth	No	2 yrs.
119	B	36	Sole	Recent appearance	Few days	Yes	1 yr.
147	C	42	Between 2nd and 3rd toes	Growth	Since birth	Yes	8 yrs.
150	C	41	Toe	Irritation	10 yrs.	Yes	6 yrs.
154	C	50	Cheek	Incidental	Since birth	No	8 yrs.
169	C	59	Back	Incidental	More than 20 yrs.	No	17 yrs.

* Classed as recent growth because of recent appearance.

indicated. If the patients' histories are correct there is no clear-cut rule, for some of these nevi were stated to be of short duration and others were stated to have been present since birth or childhood, or for an indefinitely long period. However, of the 4 nevi of adults of types A and B in which there is clinical information, there is only one which is stated to have been present since birth. Of the C type, 6 of 9 were said to have been present from birth. This is not appreciably lower than the average of the entire series.

Nevi of Hands and Feet. Nevi which deviate from the trend are commonly of the hands and feet, and a separate analysis of these is indicated. The peculiar tendencies of nevi of the distal parts of the extremities to be of the flat ("narrow stratified") type with junctional proliferation in adult life have been noted earlier in this study. Nevertheless, it was shown that there are similarities in the trend to nevi in general. In Table XX the analysis is confined to nevi of the hands and feet, omitting legs and forearms.

In patients beyond the age of 20 years there is a higher incidence of history of growth (including recent appearance) than for all other nevi in adults. For those with nevi of the hands and feet there were 7 of 17, or 41 per cent, who gave this history, while for all other nevi of adults for which there was the necessary information there were 30 of 99, or 30 per cent. In such a small series the difference is not significant.

The incidence, in adults, of short duration is a little higher in this group of nevi than with nevi of other locations. In 4 of 17, or 23.5 per cent, of these cases in which there is clinical information, the duration was significantly shorter than the age of the patient. This is to be compared with 13 of 99 cases, or 13 per cent, in all other nevi of adults in which there is clinical information. The series is small and the difference is not significant.

The above data concerning growth and duration must be weighted by the consideration that there is a special selection for surgical removal in these cases. Nevi of the feet and hands were less frequently removed incidentally and more frequently removed because the patient was aware of growth. In contrast, in cases of nevi of the thorax which were often removed incidentally during an abdominal operation, the patient may not have been aware of the nevus and its growth characteristics.

The eventual trend of nevi of hands and feet in this series is shown in Table XXI which summarizes the appearance of nevi of hands and feet of all ages. It is seen that among nevi located on hands or feet there is a trend toward diminution of the incidence of types A, B, and C between the ages of 40 and 50, and increase of incidence of types D and E. Thus,

TABLE XX
Analysis of Nevi of Hands and Fingers, Feet and Toes

Case no.	Type of nevus	Age	Location	Reason for removal	Stated duration	Recent growth	Follow-up
27	B	6	Under toe	Growth	Age 0-9 years Since birth	Yes	7 yrs.
30	B	2	Hand	Irritation	Since birth	Yes	6 mos.
57	D	14	Dorsum hand	Incidental	Age 10-19 years Since birth	No	7 yrs.
58	C	12	Dorsum foot	Bleeding and irritation	Since birth	No	15 yrs.
59	B	13	3rd toe	Incidental	Since birth	No	19 yrs.
60	D	12	Sole	Incidental	Since birth	No	1 yr.
61	A	12	Foot	Incidental	Since birth	No	1 yr.
62	A	12	Palm	Exposed to trauma	Since birth	Yes	6 mos.
89	E	21	Thumb	Prophylactic and cosmetic	Age 20-29 years Since childhood	No	3 yrs.
90	D	25	Toe	Unknown	Unknown	Unknown	Unknown
91	A	25	Hand	Unknown	Unknown	Unknown	Unknown
92	B	29	5th toe	Irritation	15 yrs.	No	5 yrs.
94	D	29	Under 2nd toe	Incidental	Since birth	No	1 yr.
115	A	37	Sole	Incidental	Age 30-39 years 1 yr.	Yes*	1 yr.
116	C	37	Toe	Incidental	Since childhood	No	1 yr.
117	C	30	Toe	Growth	Since birth	Yes	2 yrs.
118	B	30	Toe	Incidental	Since birth	No	2 yrs.
119	B	36	Sole	Recent appearance	Few days	Yes	1 yr.
147	C	42	Between 2nd and 3rd toes	Growth	Age 40-49 years Since birth	Yes	8 yrs.
148	E	48	Toe	Incidental	20 yrs.	No	4 yrs.
149	D	41	Toe	Irritation	10 yrs.	Yes	6 yrs.
150	C	41	Sole	Irritation	10 yrs.	Yes	6 yrs.
151	D	48	Sole	Irritation	A number of yrs.	No	5 yrs.
152	D	40	Toe	Incidental	As long as can remember	No	1 yr.
153	E	44	Hand	Incidental	10 or more yrs.	No	10 yrs.
179	E	51	Between toes	Growth	Age 50-59 years Since birth	Yes	13 yrs.
181	D	53	Under great toe	Incidental	Since birth	No	10 yrs.

* Classed as recent growth because of recent appearance.

in this series there is an eventual trend for nevi of hands and feet to lose junctional proliferation and for the cells to differentiate to fibrillar forms, although usually at an older age than is true of nevi of other sites. Study of a larger series of nevi of hands and feet is indicated for these results are not conclusive. It is disturbing that there is a scarcity

TABLE XXI

Summary of Histologic Appearance of Nevi of the Hands and Feet at Different Ages

Age group (years)	Type of nevus				
	A	B	C	D	E
0-4	0	1	0	0	0
5-9	0	1	0	0	0
10-14	2	1	1	2	0
15-19	No cases				
20-29	1	1	0	2	1
30-39	1	2	2	0	0
40-49	0	0	2	3	2
50-59	0	0	0	1	1
60-	No cases				

of benign nevi from the hands and feet of patients older than 50 years (we obtained only 2 cases), yet melanoblastomas are common in these sites. Undoubtedly the number is modified by the reasons for removal of a nevus. Most nevi in this series were removed incidentally and incidental removal of a nevus of the hand or foot during a major surgical operation will occur but rarely. Further, if a patient has tolerated such a nevus for 40 or 50 years he probably will not have it removed for cosmetic reasons.

Significance of Junctional Proliferation in Nevi of Adults. As pointed out earlier, the data thus far presented comprise only the first step in the analysis of this problem. Several points are evident at this time, however. The presence of junctional proliferation of moderate to marked degree in adult life, especially in young adult life, is to be expected in a minority of cases and of a slight degree in a greater number. There is no sharp distinction of such nevi from all others. There is no age at which junctional proliferation abruptly stops. Therefore, junctional proliferation does not in itself mean a "precancerous" state. A marked deviation from the trend, however, in the degree of this proliferation or in the presence of other variations, as noted in the next paragraph, raises the question of melanoblastoma.

Nevi, of adults, which consist of junctional and intra-epidermal cells almost entirely (type A), are disturbing to the pathologist and although the data submitted do not fully substantiate the conclusion in all instances, it is still suspected that these histologic characteristics indicate recent origin and growth. The other alternative is that a nevus resembling

that of early childhood can persist without further differentiation for as long as 30 to 40 years. Finding nevi (benign) of this type after age 40 is decidedly infrequent. Although the pathologist is guarded in excluding melanoblastoma in these cases, it is thought that until more conclusive evidence is obtained, such a diagnosis must rest on additional observations, including (a) excessively large, irregularly scattered or otherwise bizarre masses or nests of cells at the dermo-epidermal junction, (b) deep penetration of large cells without differentiation to small nevus cells and fibrillar forms, (c) more mitotic figures than are usual, (d) atypical and pleomorphic cells, (e) invasion, and (f) inflammation, other than folliculitis, which is not accounted for by trauma.

SUMMARY

There are progressive changes in the histologic appearance of nevi throughout life. The features which change most noticeably are size, number of nevus cells, proliferation of cells in the epidermis and at the dermo-epidermal junction, number of mitotic figures, and presence of fibrils and nerve-like elements. In most instances, an approximate correlation of the histologic appearance with the age of the patient can be made by an evaluation of these features.

Judged from the transitions noted in the different age groups, nevus cells appear to differentiate slowly from foci of clear cells found in the epidermis and follicles and along sweat glands. Further differentiation, principally in adult life, leads to the formation of fusiform cells with fibrils which in many instances resemble neurofibrils and tactile corpuscles. Such structures are therefore to be considered the final stage of differentiation of nevus cells, not the source of nevus cells. That the foci in the epidermis, follicles, and sweat glands are the only source of nevus cells is favored but not proved.

There are exceptions to the general trend. Nevi of children may resemble those of early adult life. Nevi of adults, usually in the third and fourth decades, may resemble nevi of childhood. The latter exception is notable in regard to nevi of the hands and feet. However, in this series the trend of nevi in middle age in these sites is similar to the trend of nevi in general. Final conclusions must be based on a larger series.

Junctional proliferation in nevi of adults does not in itself indicate melanoblastoma. There are an expected incidence and degree of such proliferation at various ages. Certain additional criteria must be fulfilled before a histologic diagnosis of melanoblastoma is warranted.

In adults the occurrence of nevi which morphologically resemble those of childhood leads to the suspicion that they are incipient and

growing, but clinical evidence obtained in this analysis of their duration and rate of growth is variable and conflicting, permitting no final conclusion. Evaluation must await further study.

Nevi vary in appearance according to location. A notable modifying factor is the number of hair follicles and sweat glands in the various cutaneous sites. While most nevi have nevus cells in a superficial stratum beneath the epidermis, deeply placed nevus cells tend to have a perifollicular and periglandular distribution. Diffusely scattered, deeply placed nevus cells also occur.

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[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 177

- FIG. 1. Nevus of abdomen of a male, 6 years of age. There is proliferation of large pigmented cells at and beneath the dermo-epidermal junction. One mitotic figure is shown. $\times 445$.
- FIG. 2. Nevus of thorax of a female, 42 years old. Fibrillar structures resemble tactile corpuscles. $\times 312$.

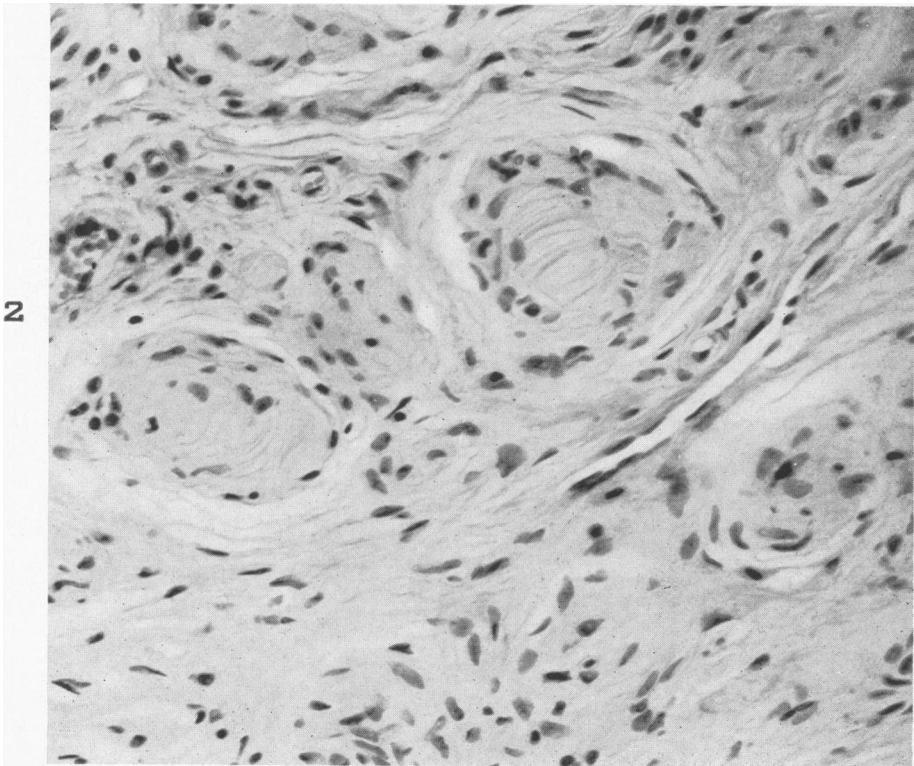
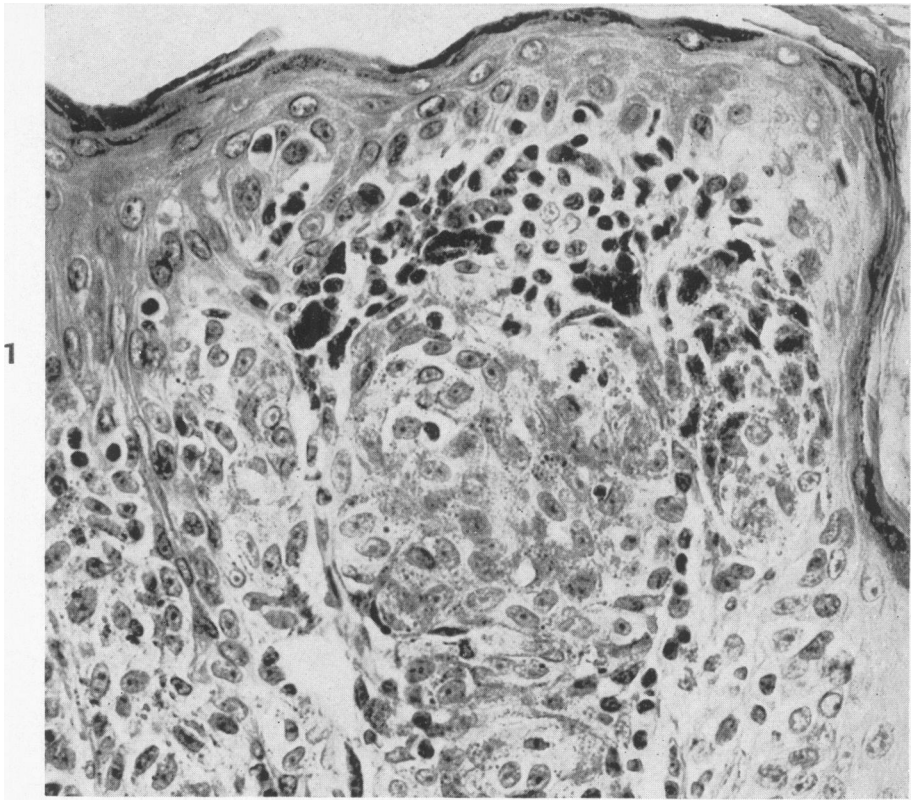
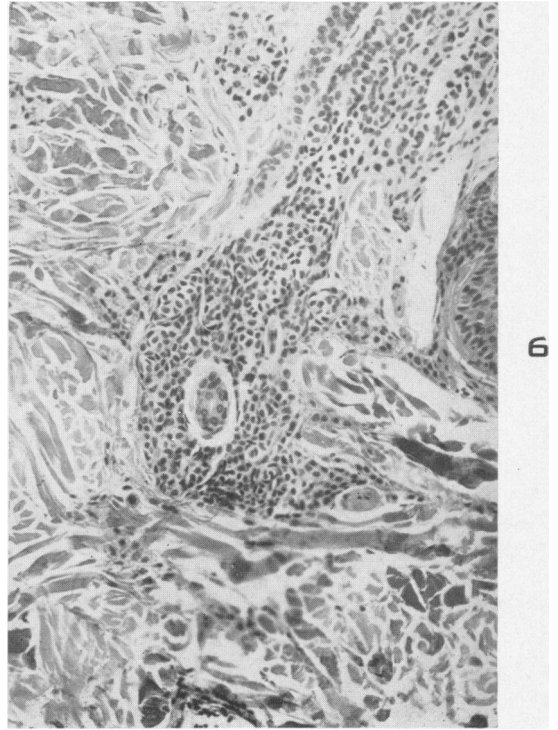
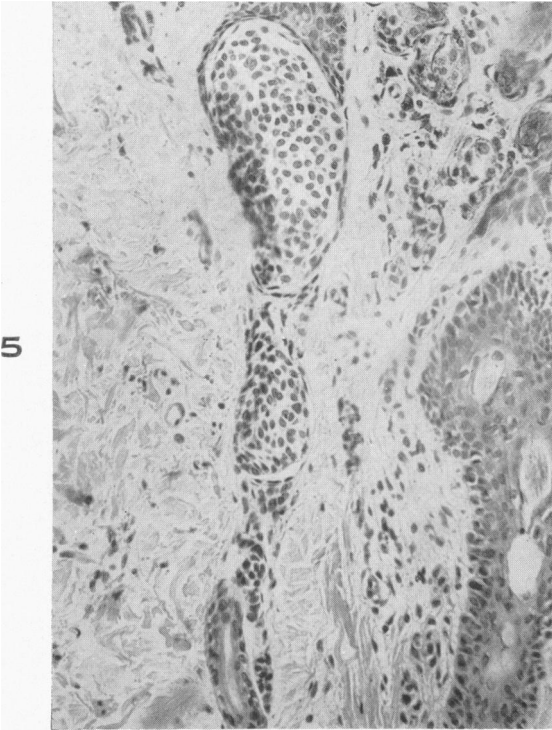
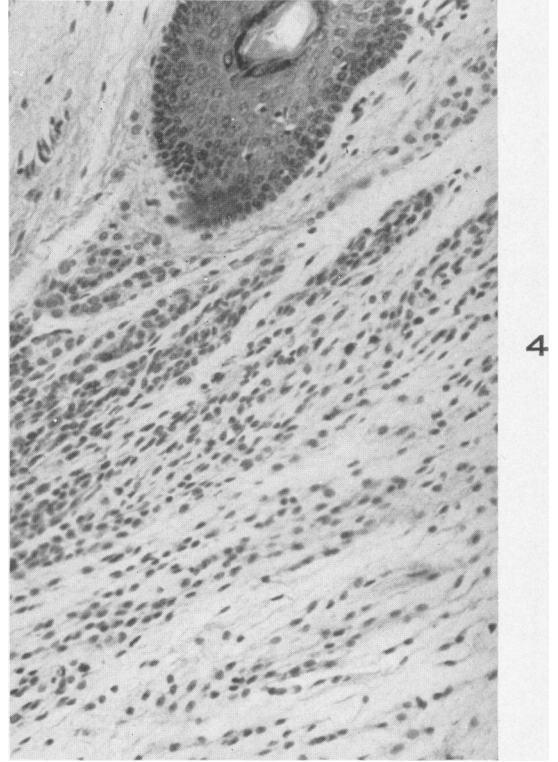
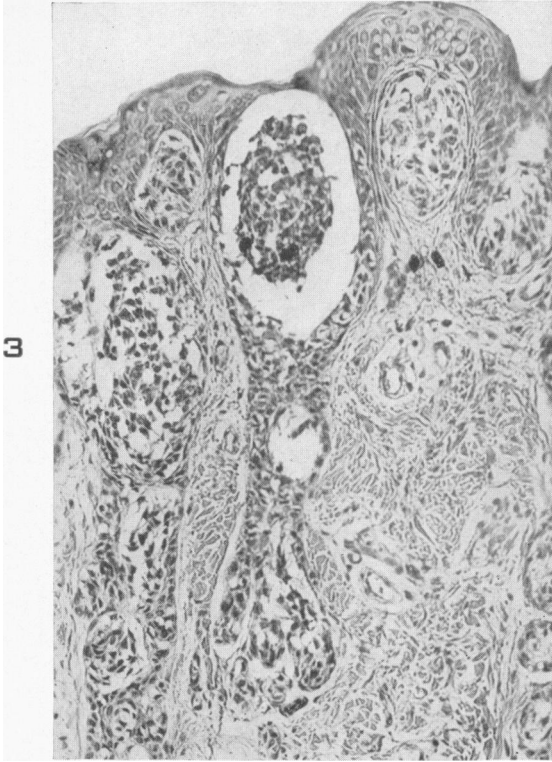


PLATE 178

- FIG. 3. Nevus of face of a female, aged 12 weeks. Clear cells are present in clumps within the epidermis and along the hair follicles. $\times 154$.
- FIG. 4. Nevus of a female, 37 years old. Small round nevus cells and fusiform fibrillar nevus cells are present. $\times 186$.
- FIG. 5. Nevus of thorax of a male, aged 6 years. Clear cells occur in clumps along a sweat gland. $\times 169$.
- FIG. 6. Nevus of scalp of a female, 18 years of age, with nevus cells distributed about a sweat gland.



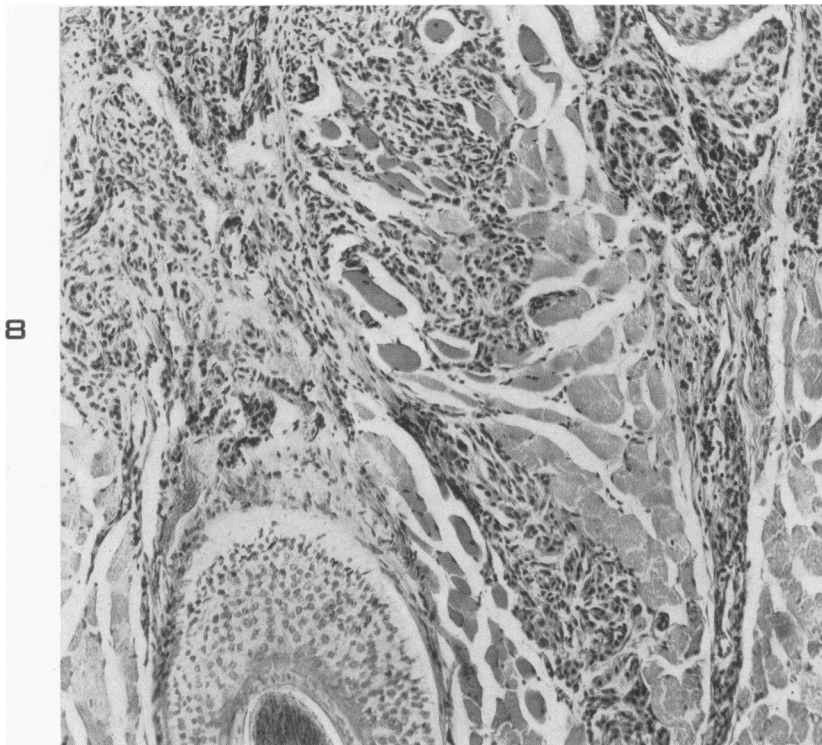
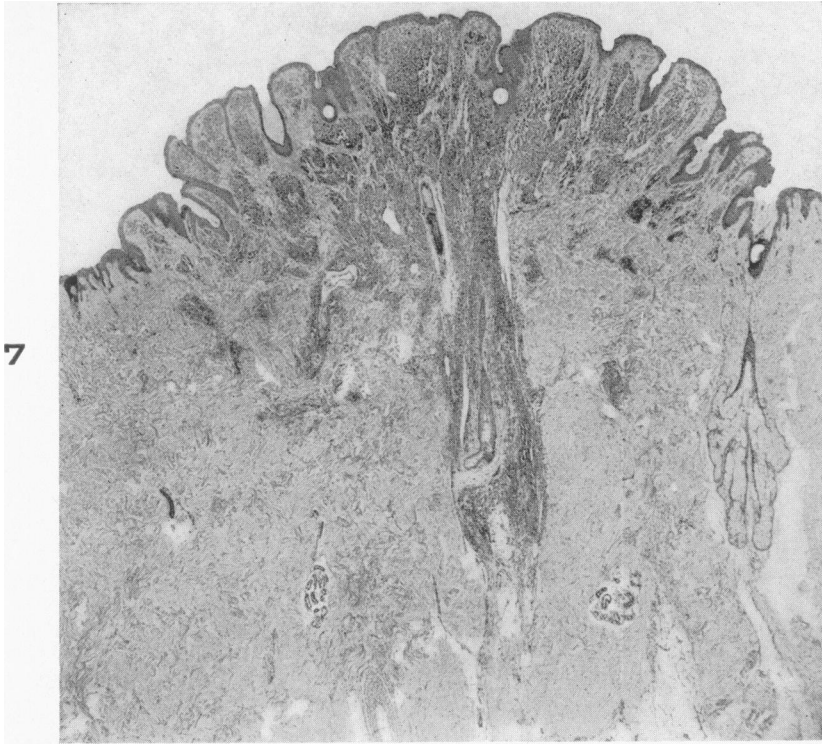
Lund and Stobbe

Natural History of the Pigmented Nevus

PLATE 179

FIG. 7. Nevus of neck of a female, 19 years old. The deep cells have a perifollicular distribution. $\times 18$.

FIG. 8. Nevus of lower eyelid of a male, aged 22 years. Nevus cells are found among striated muscle fibers. There has been no recurrence in 18 years. $\times 109$.



Lund and Stobbe

Natural History of the Pigmented Nevus

PLATE 180

- FIG. 9. Nevus of sole of a female, 37 years of age. Clear cells are present in clumps in epidermis. No nevus cells are found in the corium. $\times 150$.
- FIG. 10. Nevus of sole of a female, 48 years of age. Nevus cells are present in the corium. There is slight dermo-epidermal proliferation. $\times 150$.
- FIG. 11. Nevus between toes of a male, aged 41 years. Nevus cells are present in the corium. There is no junctional proliferation. $\times 79$.

