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Histological type and biological behavior of primary cutaneous malignant melanoma

1. An analysis of 1916 cases

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Summary. In 1916 patients with primary malignant melanoma of the skin (excluding palms, soles, and nailbeds) the primary lesions were reviewed microscopically and classified according to Clark's system into lentigo maligna melanoma (85), superficial spreading melanoma (1234), and nodular melanoma (513). Differentiation between the types was not possible in 84 melanomas (4%). By correlating type of melanoma with various clinical and histological features, it was found that the 3 types differed significantly from one another with regard to growth rate of tumor, antecedent nevus, dominant type of invasive tumor cell, and prognosis. The study thus supported the basic principle of the classification employed, that the 3 histological types represent distinct entities of cutaneous melanoma with different clinical, cellular, and behavioral characteristics. As originally described by Clark, the growth rate was greatest for nodular melanoma, followed by superficial spreading melanoma, and least for lentigo maligna melanoma. It is recommended that this classification be employed in the histological typing of cutaneous melanoma as 1) it is readily applied to the vast majority of melanomas, and 2) it seems to delineate separate clinico-pathologic entities of cutaneous melanoma, which might be correlated with aetiological differences.

Key words: Cutaneous malignant melanoma – Histological types

In 1966 the Australian Committee of Pathologists recommended a classification of cutaneous melanomas based on clinical and histological information. It distinguished between melanomas which had arisen in 1) benign nevi, 2) pre-malignant melanosis, 3) Hutchinson's melanotic freckle, and 4) previously blemish-free skin (McGovern et al. 1967).

In 1967 Clark described 4 different types of melanoma, based on a retrospective clinico-histological study of 96 patients with primary cutaneous

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melanoma. In 1969 Clark et al. reduced the number to 3 distinct types, namely lentigo maligna melanoma (LMM), superficial spreading melanoma (SSM), and nodular melanoma (NM) in order of increasing growth rate and malignancy. Apart from rare exceptions, Clark defined the cutaneous melanomas as malignant proliferations of the epidermal melanocytes. Consequently the classification was independent of the possible presence of an antecedent nevus. In his classification, Clark isolated a very aggressive type of melanoma, NM, which was invasive from the onset without an in-situ phase, i.e. without initial intra-epidermal malignant proliferation of the melanocytes.

The meeting of international pathologists in Sydney in 1972 accepted the melanoma classification of Clark, although recommending a slightly different nomenclature (McGovern et al. 1973). The fundamental principle of the classification was that the 3 types represented distinctive clinico-pathological entities with different clinical, cellular, and behavioral characteristics (Clark 1967; Clark et al. 1969, 1972, 1975; Elder et al. 1979).

However, in 1980 Ackerman questioned the existence of different entities of cutaneous malignant melanoma with specific clinico-histological features, as well as melanomas without an in-situ phase.

In the present study the results of a retrospective histological classification of the primary melanomas in 1916 patients have been correlated with currently recorded historical data in order to evaluate the following substantial problems:

1) Is it possible to classify histologically the cutaneous melanomas along the lines described by Clark et al. (1969) and McGovern et al. (1973)?

2. Is there evidence that the different histological types represent distinct clinico-pathological entities of cutaneous melanoma?

The melanomas located on the palm of the hand, the sole of the foot, and the nailbeds will be the subject of a later paper, as their histological classification offers special problems following the description by Reed of a new type of melanoma (acral lentiginous melanoma) in these locations (Clark et al. 1975; Reed 1976).

Material and methods

During the period January 1949 to April 1978, 2469 patients were treated and subsequently followed up for cutaneous melanoma at the Finsen Institute. In 2012 of the patients the histological material from the primary cutaneous melanoma was available and suitable for microscopic reclassification, which was done by one person (KS). Histologically all the 2012 lesions were primary cutaneous melanomas with obvious dermal invasion. In 86 out of 2012 patients the melanoma was located on palmar, plantar, and sub-/parungual areas.

The present study deals with the remaining 1926 cutaneous melanomas. In 1610 out of 1926 patients (84%) the primary lesion was excised at the Finsen Institute, whereas 316 patients (16%) were admitted for extended excision after primary total excision elsewhere. For the microscopic examination the original sections were used together with 4 new haematoxylin-eosin stained sections. If the primary melanoma or parts of it were excised elsewhere the original sections or newly prepared sections were borrowed.

Generally, the primary lesions were treated with wide excision at a minimum distance of 5 cm down to but not including the fascia. On the face the tumors were excised at a

distance of 2 cm. Lymph nodes were dissected where clinically enlarged. Postoperatively the patients were followed up regularly at the Finsen Institute for up to 10 years or more.

The clinical reporting included

1. *Site of tumor*
2. *Sex and age of patient*
3. *Presence and duration of antecedent nevus*

During the whole period, from 1949 to 1978, the patients were carefully questioned at their first examination at the Finsen Institute, whether the melanoma was arisen from an antecedent nevus, and if so, how long time the nevus had been present before the melanoma developed. The duration of a possible antecedent lesion was subgrouped as follows:

a) Less than 2 years indicating *no antecedent nevus,* as pre-existing lesions of less than 2 years duration were regarded as malignant from their onset.
b) 2–5 years, i.e. nevus of *few years duration.*
c) More than 5 years but not lifelong, i.e. nevus of *many years duration.*
d) *Lifelong,* i.e. nevus which had been present as long as the patient could recall.
e) *Uncertain.*

4. *Duration of symptoms from the melanoma*

All patients were carefully asked when they became aware of a new tumor or an obvious change in an existing nevus such as obvious growth, color change, bleeding etc. The following grading was employed:

a) Less than 1 year.
b) 1–3 years.
c) More than 3 years.
d) Uncertain.

5. *Clinical stage*

Clinical stage as described by Olsen (1966) was:

a) Stage I: Localized disease.
b) Stage II: Regional metastases.
c) Stage III: Remote metastases.

Histological evaluation of the melanomas included

1. *Histological type of melanoma*

Histological type of melanoma according to Clark et al. (1969) and McGovern et al. (1973) as previously described by Søndergaard (1980).

a) *Lentigo maligna melanoma (LMM)* (Fig. 1) characterized by a peripheral continuous proliferation of pleomorphic melanocytes in the basal layer of the epidermis extending more than 3 rete ridges from areas of clear dermal invasion. In areas with no dermal invasion, the epidermal invasion was minimal and junctional nesting not common. Epidermal atrophy and solar dermal elastosis were present.

b) *Superficial spreading melanoma (SSM)* (Fig. 2) characterized by Pagetoid extension and/or marked junctional nesting of malignant melanocytes extending more than 3 rete ridges from areas of clear dermal invasion. Epidermal hyperplasia was common.

c) *Nodular melanoma (NM)* (Fig. 3), being an invasive melanoma with peripheral intra-epidermal spread of tumor cells extending less than 4 rete ridges from areas of dermal invasion.

d) *Melanomas of unclassifiable type (UM),* designating melanomas not included in the above mentioned groups.

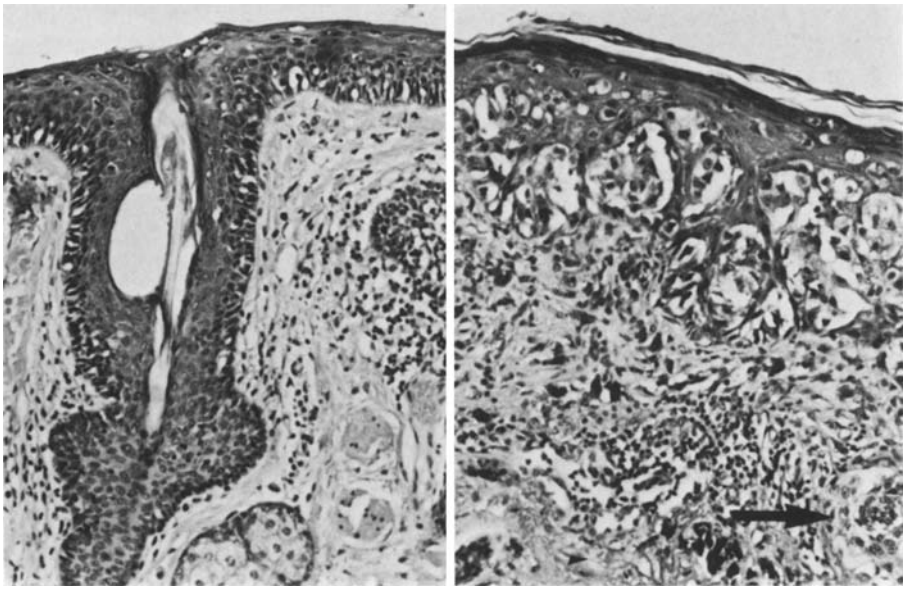

Fig. 1. Lentigo maligna melanoma adjacent to an area of dermal invasion. Face. There is a linear proliferation of pleomorphic melanocytes in the basal layer of the epidermis with involvement of the hair follicle. There is solar degeneration of the dermis. Haematoxylin and eosin. × 130

Fig. 2. Superficial spreading melanoma. Face. There is Pagetoid growth of tumor cells in the epidermis adjacent to a focus of dermal invasion (*arrow*). There is solar degeneration of the epidermis. Haematoxylin and eosin. × 130

2. *Type of the dominant invasive tumor cell:*

a) Nevoid.
b) Epithelioid.
c) Spindle.
d) Ballon.
e) Equal mixture of two or more cell types.

3. *Presence of obviously benign nevus cells*

4. *Maximal tumor thickness*

Maximal tumor thickness measured in mm according to Breslow (1970) as previously described (Søndergaard 1980).

Statistical analysis

The cumulative survival rates were calculated by the life table method and compared by the logrank test (Peto et al. 1977). Where appropriate the Chi square test was used. Significance was assessed at $P < 0.05$.

Results

In 10 of the 1926 cases the available histological material was not suitable for evaluation of histological type as the normal epidermis surrounding the melanoma was not present in the sections. In 1851 (97%) of the remain-

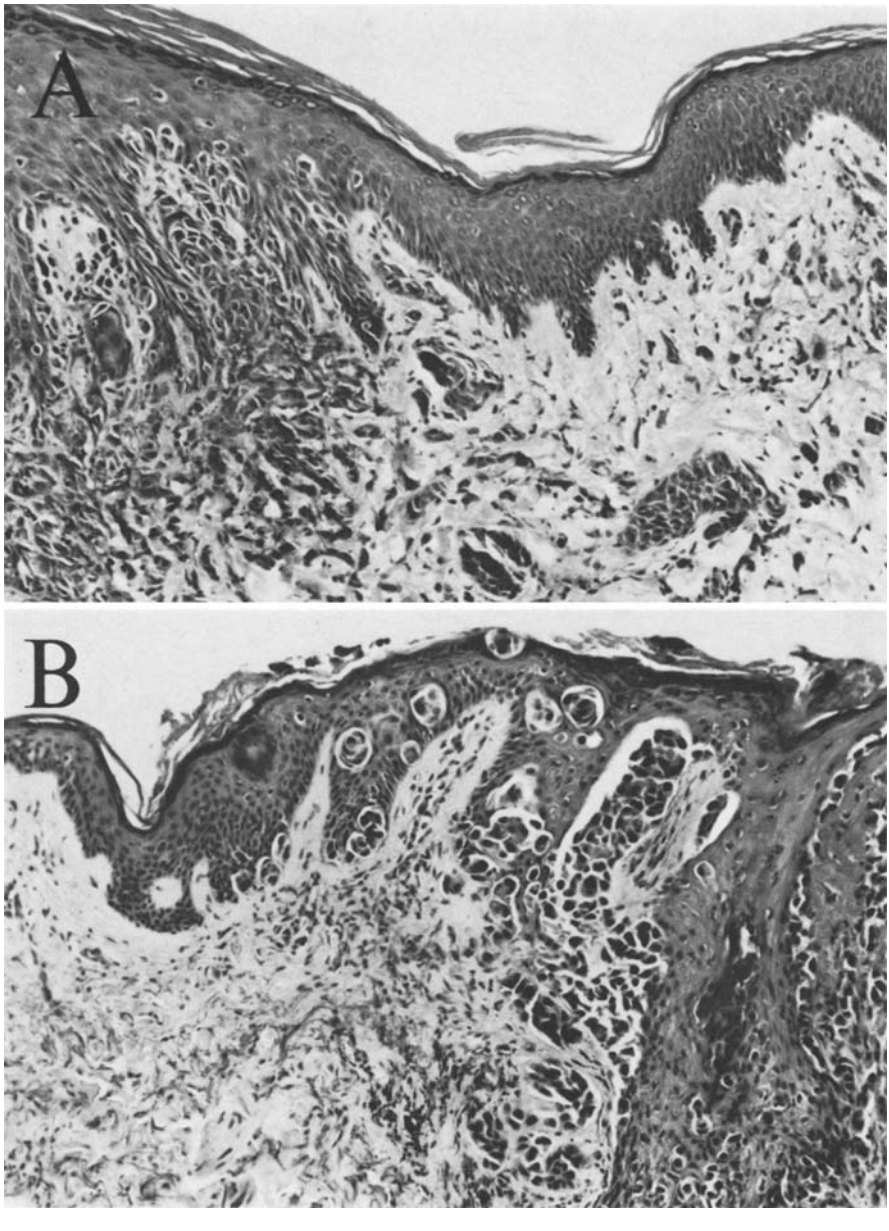

Fig. 3A, B. Nodular melanoma. **A** Upper arm. There is no intra-epidermal spread of tumor cells surrounding the invasive part of melanoma. **B** Trunc. There is an intra-epidermal spread of tumor cells extending less than 4 rete ridges from areas of dermal invasion. Haematoxylin and eosin. ×130

ing 1916 lesions at least one cross-section included the surrounding epidermis from two opposite sides of the tumor. In 65 (3%) of the cases it was possible to investigate the epidermis to only one side of tumor. As shown in Table 1 two or more cross-sections were available from more than half of the tumors.

Table 1. Number of cross-sections per lesion available for the histological classification of 1916 cutaneous melanomas

Number of cross-sections per melanoma	Number of melanomas
1	941
2	517
3	211
4	102
5 or more	145
Total	1,916

Table 2. Various clinical and histological features correlated with histological type of melanoma in 1916 patients

Histological type of melanoma	Duration of antecedent nevus					Duration of history of melanoma			
	0–2 years	2–5 years	>5 years	life-long	uncer-tain	<1 years	1–3 years	>3 years	uncer-tain
LMM	17	8	46	10	4	57	17	4	7
SSM	271	116	358	398	91	829	259	38	108
NM	170	36	126	139	42	385	73	6	49
SSM-LMM	7	1	9	3	2	10	5	1	6
NM-ACM	24	2	14	14	8	43	12	1	6
Total	489	163	553	564	147	1,324	366	50	176

Type of dominant invasive tumor cells					Tumor thickness in mm (average)	Total
Nevoid	Epithel.	Spindle	Balloon	Mixture		
2	22	32	0	29	2.46	85
117	770	54	0	293	2.20	1,234
5	314	35	0	159	4.48	513
2	8	3	0	9	1.02	22
3	36	3	0	20	4.30	62
129	1,150	127	0	510	2.87	1,916

Of 1916 patients 688 (36%) were males and 1228 (64%) females. 1694 patients were in clinical stage I, 181 in stage II, and 41 in stage III.

Table 2 shows that out of 1916 melanomas, 85 were LMM, 1234 SSM, 513 NM, and 84 of unclassifiable type (UM). 22 (*SSM-LMM*) histologically were intermediate between SSM and LMM with solar elastosis of the dermis and lentiginous proliferation of atypical melanocytes as well as areas with moderate Pagetoid extension of tumor cells in the epidermis adjacent to

Table 3. Duration of symptoms of SSM and NM in various locations

	Duration of symptoms of melanoma			
	SSM		NM	
	<1 year	>1 year	<1 year	>1 year
Head	74	36	64	15
Neck	21	6	12	1
Trunk	322	90	129	17
Upper arm	58	21	41	11
Lower arm	31	14	19	3
Thigh	89	16	33	10
Lower leg	193	103	70	16
Hand and foot (excl. palm, sole and nailbeds)	41	11	17	6
Total	829	297	385	79

areas of dermal invasion. In the remaining 62 melanomas (*NM-ACM*) it was uncertain whether or not the adjacent intra-epidermal proliferation of tumor cells extended more than 3 rete ridges beyond areas of clear dermal invasion, i.e. whether the melanomas were NM or melanomas with adjacent intra-epidermal component (ACM).

As shown in Table 2 no antecedent nevus was found in 489 patients. This group included patients reporting pre-existing lesions of less than 2 years' duration, as such lesions were regarded as malignant from their beginning. If antecedent nevi were present, their duration was 2–5 years in 163 patients, many years (more than 5 years) in 553 patient, lifelong in 564 patients, and uncertain in 147 patients. Significantly more patients with SSM (398/1143, 35%) had a lifelong antecedent nevus than had patients with NM (139/471, 30%) ($p<0.05$) and LMM (10/81, 12%) ($p<0.0005$). Significantly more patients with SSM (756/1143, 66%) than with NM (265/471, 56%) had an antecedent nevus of more than 5 years' duration or lifelong duration ($p<0.0005$).

Clearly benign nevus cells were demonstrated in 9% (177/1916) of the melanomas by the microscopic examination. Nevus cells were found significantly more often in SSM 136/1234, 11%) than in both NM (26/513, 5%) ($p<0.0005$) and LMM (3/85, 4%) ($p<0.05$).

Significantly more NM (385/464, 83%) than SSM (829/1126, 74%) had a history of less than one year's duration ($p<0.0005$). Also on the lower leg ($p<0.005$), head and neck ($p<0.025$), and trunk ($p<0.01$) significantly more NM than SSM had a history of less than one year's duration, whereas no statistical differences were found in the remaining regions shown in Table 3.

Table 4A shows the correlation between the duration of LMM and the presence of antecedent nevi based on the information from 85 patients with

Table 4. Duration of history of melanoma correlated with duration of a possible antecedent nevus in 85 patients with LMM *before correction* (**A**) and *after correction*[a] (**B**)

Duration of history of LMM	Duration of a possible antecedent nevus					Total
	0–2 years	2–5 years	>5 years	lifelong	uncertain	
A *No correction:*						
≦3 years	15	8	42	8	1	74
>3 years	0	0	3	1	0	4
uncertain	2	0	1	1	3	7
Total	17	8	46	10	4	85
B *After correction*[a]*:*						
≦3 years	15	8	5	8	1	37
>3 years	37	0	3	1	0	41
uncertain	2	0	1	1	3	7
Total	54	8	9	10	4	85

[a] The correction was based on the assumption that the number of LMM which had arisen from antecedent nevi of many years' duration (i.e. >5 years) was 0.9 times the number of LMM which had arisen from lifelong nevi, i.e. 9 (**B**) instead of 46 (**A**)

LMM. 57% (46/81) of the patients stated that the melanoma arose from a nevus that had been present for many years.

Table 4B shows the corrected duration of LMM based on the assumption that the number of LMM that had really arisen from nevi of more than 5 years' duration was 0.9 times the number of LMM that had arisen from lifelong nevi as with both SSM and NM (Table 2). On that assumption, only 9 LMM (0.9×10) arose from nevi of many years' duration. The subtraction of 1 LMM with uncertain duration, as well as 3 LMM with a history of more than 3 years, gave the result that only 5 LMM with symptoms of less than 3 years' duration really arose from antecedent nevi, whereas the remaining 37 LMM were slowly growing LMM, malignant from their start. Thus significantly more LMM (41/78, 53%) (Table 4B) had a history of more than 3 years' duration than both SSM (38/1126, 3%) ($p < 0.0005$) and NM (6/464, 1%) ($p < 0.0005$).

The average tumor thickness was 2.46 mm for LMM and 2.20 mm for SSM. NM was about twice as thick as LMM and SSM, as shown in Table 2 (4.48 mm).

As seen in Table 2, significantly more LMM (32/85, 38%) than SSM and NM (89/1747, 5%) ($p < 0.0005$) had spindle cells as the dominant invasive tumor cell.

Tables 5 and 6 show the sex- and age-distribution and the locations of the various types of melanoma. In contrast to SSM and NM, LMM was seen almost exclusively on sun-exposed skin in elderly persons.

Table 5. Histological type correlated with sex and age of 1916 patients with cutaneous melanoma

Age of patients (years)	Histological type										Total	
	LMM		SSM		NM		SSM-LMM		NM-ACM			
	M	F	M	F	M	F	M	F	M	F	M	F
0–14	0	0	0	3	0	0	0	0	0	0	0	3
15–24	0	0	13	21	9	16	0	0	2	2	24	39
25–34	0	0	53	104	23	44	0	0	3	5	79	153
35–44	1	1	75	188	47	50	0	2	4	6	127	247
45–54	5	4	104	205	54	50	1	1	1	9	165	269
55–64	10	5	80	176	42	56	3	4	1	8	136	249
65–74	9	25	55	95	26	48	7	1	8	7	105	176
75–84	6	14	18	39	17	20	2	1	2	4	45	78
85 or more	0	5	1	4	6	5	0	0	0	0	7	14
Total	31	54	399	835	224	289	13	9	21	41	688	1,228

Table 6. Histological type correlated with site of primary cutaneous melanoma in 688 males and 1228 females

Site of primary melanoma	Histological type of melanoma										Total	
	LMM		SSM		NM		SSM-LMM		NM-ACM			
	M	F	M	F	M	F	M	F	M	F	M	F
Head	27	52	42	76	42	42	10	5	6	9	127	184
Neck	1	1	6	22	6	10	3	1	1	0	17	34
Trunk	2	0	235	222	113	50	0	0	10	7	360	279
Upper arm	0	0	25	63	16	39	0	0	2	5	43	107
Lower arm	0	0	17	36	3	22	0	1	0	0	20	59
Hand[a]	0	1	1	8	1	5	0	0	0	0	2	14
Thigh	1	0	30	81	15	31	0	0	0	3	46	115
Lower leg	0	0	30	290	20	80	0	2	1	15	51	387
Foot[a]	0	0	13	37	8	10	0	0	1	2	22	49
Total	31	54	399	835	224	289	13	9	21	41	688	1,228

[a] Excluding melanomas of palm, sole, and nailbeds

As shown in Fig. 4 the 5-year survival (10-year survival) for the different types of melanoma was LMM 89% (79%), SSM 76% (69%), NM 54% (46%), SSM-LMM 82% (82%), and NM-ACM 60% (54%). The differences were highly significant ($p = 0.0001$).

The survival rates associated with the dominant cell type of LMM, SSM, and NM were calculated by the life table method and compared by the logrank test. In Table 7 the 5-year survival rates and the p-values are shown. In both SSM ($p < 0.0005$) and NM ($p < 0.025$) the prognosis was significantly

Table 7. Number of patients and 5-year survival rate corresponding with the dominant invasive tumor cell and histological type of melanoma

Dominant type of tumor cell	Histological type of melanoma						p (d.f.* = 2)	Total	
	LMM		SSM		NM			Number	5-year survival
	Number	5-year survival	Number	5-year survival	Number	5-year survival			
Nevoid	2	100%	117	90%	5	100%	>0.5	124	91%
Spindle	32	90%	54	80%	35	75%	>0.1	121	80%
Epithelioid	22	90%	770	72%	314	47%	<0.0005	1106	65%
Mixture	29	85%	293	72%	159	55%	<0.0005	481	68%
p (d.f.* = 3)		>0.5		<0.0005		<0.025			<0.0001

* d.f. = degrees of freedom

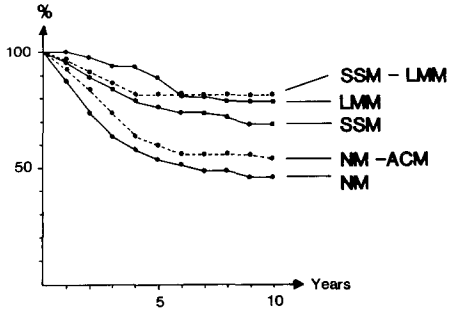

Fig. 4. Cumulative survival rates corresponding to histological types of melanoma

influenced by dominant cell type. The nevoid cell type was correlated with the best prognosis, followed by the spindle cell type, and then the mixed and the epithelioid cell type. It was also found that in melanomas of epithelioid cell type ($p<0.0005$) and mixed cell type ($p<0.0005$) the prognosis was significantly influenced by type of melanoma. LMM was associated with the best prognosis, followed by SSM, and then NM. The same was seen in the spindle cell type of melanoma, but the difference was not statistically significant ($p>0.1$). In the nevoid cell type the influence of melanoma type was difficult to evaluate as only 2 LMM and 5 NM were of this cell type.

Discussion

A statement of the frequency of melanomas arising from pre-existing nevi can only be approximate and depends on the patient's own powers of observation, his memory, and the site of the tumor. The same applies to the assessment of how long a pre-existing nevus has been present, and when the patient became aware of the malignant melanoma (i.e. obvious growth, color changes etc. of a pre-existing lesion or the origin of a new tumor).

During the first examination at the Finsen Institute all patients were carefully questioned about the duration of a possible antecedent nevus as well as the duration of the melanoma. It was found that 63% (1117/1769) of the melanomas arose from nevi which had been present either for many years (i.e. more than 5 years) or as long as the patient could recall, whereas 28% (489/1769) of the melanomas arose "de novo". Pre-existing lesions of 2–5 years' duration were not used in the analysis as it was regarded as being uncertain whether they represented pre-existing nevi or early-phase melanomas.

The present findings are in accordance with the estimates of the correlation between melanomas and pre-existing lesions given by other authors. In her study of 500 patients, Olsen (1966) found that 62% of the melanomas developed in congenital nevi or in nevi which had been present for many years. In 220 patients Petersen et al. (1962) showed that 62% of the melanomas arose from pre-existing lesions, while 27% were malignant from the start. Milton (1972) reported that 66% of 824 patients noticed an antecedent skin blemish, while 29% of the melanomas arose "de novo". Similarly, Ariel (1982) found that 69% of 740 melanomas of the trunk arose from a preceding mole, whereas 31% arose "de novo".

In the present material, obviously benign intra-dermal nevus cells were demonstrated in only 9% of the melanomas. This does not imply that most melanomas did not arise from antecedent nevi, as it is not possible on histological grounds to recognize whether an antecedent junctional nevus had been present, once a melanoma has developed (McGovern 1970). In other studies the frequency of histological evidence of intra-dermal nevus cells in melanomas varied from 10% (Clark et al. 1969; Larsen 1978) to 22–27% (Cochran 1968; McGovern 1970), presumably due to different views and interpretations of what was nevus cells and what was nevoid melanoma cells.

The present study showed that 76% of the melanomas had a history of duration of less than one year, in accordance with 75% of the melanomas reported by Olsen (1966).

Bodenham (1968) and Clark (1967) found that as many as 53–57% of the melanomas had been present for more than 1–2 years before treatment. However, the results from different studies are not quite comparable as they are influenced by how antecedent nevi were distinguished from the early phase of the melanomas.

It is well established that the extension of the adjacent intra-epidermal tumor area varies from melanoma to melanoma. Thus Larsen (1978) found that 31 of 49 SSM (63%) were completely surrounded by an intra-epidermal tumor area. In 12 of 49 SSM (24%) this occupied less than 50% of the circumference. If SSM of the latter group mentioned had not been investigated by serial block technique, some of them might have been incorrectly classified as NM. If the histological material available included the surrounding normal epidermis from only one side of the tumor the risk of misclassification would increase, while, the risk would be reduced if more than one section from the tumor were available (Clark et al. 1975). However,

even on the basis of a single cross-section including the normal epidermis from two opposite sides of the melanoma, it is possible to obtain the correct histological classification in 95% of the cases, as shown by Søndergaard (1980) and Larsen (1978).

Though the present study was retrospective, the available histological material from 1916 patients with cutaneous melanomas was considered to be suitable for classification of the histological types, on the following grounds:

1. In 84% of the cases the melanomas were sectioned and the slides were made in the same laboratory, ensuring a uniform procedure.

2. In 97% of the melanomas at least one cross-section included the surrounding epidermis from 2 opposite sides of the tumor.

3. In 51% of the lesions at least 2 cross-sections were available for the microscopic examination. In 24% at least 3 cross-sections were available.

The classification of the 1916 melanomas resulted in 85 LMM, 1234 SSM, and 513 NM. 84 melanomas were unclassifiable. Two groups of unclassifiable melanomas were noted: 1) Melanomas having a non-invasive adjacent component with a position between that of SSM and that of LMM (SSM-LMM); and 2) melanomas in which it was uncertain whether or not a non-invasive adjacent component was present (NM-ACM). In the present study there were 22 SSM-LMM and 62 NM-ACM, resulting in one SSM-LMM to 4 obvious LMM, and one NM-ACM to 10 obvious NM. In all, the unclassifiable cases accounted for only 4% of the lesions. Thus the study showed that Clark's classification was readily applied to the vast majority of cutaneous melanomas.

Clark's classification rests on the hypothesis that LMM, SSM, and NM are 3 distinct clinico-pathological entities with different developmental biology and growth rates and consequently different clinical courses (Clark 1967; Clark et al. 1969, 1979; Elder et al. 1979). In NM the tumor cells invade the dermis from the beginning (vertical growth), so that no in-situ phase can be demonstrated. By comparison LMM and SSM have an initial phase in which the tumor cells spread horizontally in the epidermis and the most superficial part of the dermis (horizontal or radial growth phase). After a period of time which is considerably longer for LMM that for SSM, vertical growth takes place.

If Clark's theory is correct it should be demonstrable that in melanomas of approximately the same volume the longest duration of symptoms is found in LMM followed by SSM and then by NM. This has actually been shown by the present study.

Significantly, more patients with NM gave a history of less than one year's duration than did patients with SSM ($p < 0.0005$) (Tables 2 and 3). The difference was not caused by NM being located particularly in areas infrequently observed by the patients, as both on the lower leg ($p < 0.005$) and the head-neck ($p < 0.025$) there were significantly more NM than SSM causing complaints for less than 1 year. Also on the trunk, significantly more NM than SSM had a history of less than one year's duration ($p < 0.01$).

Table 2 shows that apparently the same duration of symptoms was atributed to both SSM and LMM. However, out of 81 LMM with known duration of antecedent nevi, 46 LMM were reported arising from long-standing nevi, in contrast to the observation of McGovern (1970, 1976) that LMM arose only infrequently from antecedent nevi. The explanation seems to be that a number of the patients confused the long initial phase of LMM with an antecedent nevus. In order to estimate that number, the assumption was made that the ratio between the number of melanomas arising from nevi of many years' duration and the number of melanomas arising from lifelong nevi was the same for LMM, SSM, and NM. In Table 2 it is seen that that ratio was 0.9 for both SSM ($358/398 = 0.9$) and NM ($126/139 = 0.9$). As Table 2 also shows that 10 LMM arose from lifelong nevi, the expected number of LMM arising from nevi lasting many years is 9 (10×0.9) instead of 46. The remaining 37 LMM were "de novo" melanomas causing symptoms for more than 5 years. In Table 4A (showing duration of symptoms and antecedent nevi in 85 LMM) these 37 LMM should consequently be taken from the group of 42 LMM with "antecedent nevus > 5 years and symptoms $\leqq 3$ years" and placed in the group of 0 LMM with "antecedent nevus 0–2 years and symptoms > 3 years". This resulted in Table 4B, showing that 53% (41/78) of LMM had a history of more than 3 years, which was significantly more frequent than both SSM and NM ($p < 0.0005$).

As tumor thickness is closely correlated to tumor volume (Breslow 1970), the average tumor volume in the present study was almost equal for LMM and SSM, whereas it was much greater for NM that for LMM and SSM. Combined with the finding that the duration of symptoms was shortest for NM, medium for SSM, and longest for LMM, it meant that the average growth rate was greatest for NM, followed by SSM and smallest for LMM.

Ackerman stated recently that from a biological point of view also NM must start with an in-situ phase and superficial spread of tumor cells like SSM (1980). In 1982 Heenan and Holman suggested that NM was just the end stage of LMM and SSM. However, other authors found that an in-situ phase is bypassed and, for practical purposes, is never seen in NM (McGovern 1976; Elder et al. 1982). It was stressed that the potential of NM for vertical growth exceeded the potential for horizontal growth by so much, that an intra-epidermal spread of tumor cells will not extend more that 3 rete ridges beyond areas of obvious dermal invasion (McGovern et al. 1973; Reed 1976; Elder et al. 1979; Levene 1980).

The present study was unable to evaluate the constancy of histological type during growth of melanoma. Nevertheless it was demonstrated that NM was not simply the end of a long-standing SSM, in which the adjacent non-invasive component was destroyed in time, as the average history of duration of NM was shorter than that of SSM.

In addition to magnitude of growth rate, the present study has demonstrated that LMM, SSM, and NM also differed from one another in the following ways:

SSM arose significantly more frequently from antecedent nevi than did NM ($p<0.0005$), which on the other hand arose more frequently from nevi than did LMM ($p<0.0005$).

Spindle cells were much more often the dominant type of tumor cell in LMM than in SSM and NM ($p<0.0005$), as found by others (Larsen and Grude 1978 B).

As in most other studies, SSM was more prevalent than LMM and NM in both sexes, and LMM was almost exclusively found on sun-exposed skin in elderly persons, in contrast to SSM and NM (Clark et al. 1975; Larsen and Grude 1978 A; Eldh et al. 1978; Drzewiecki et al. 1980; McGovern et al. 1979, 1980).

As shown by others LMM was correlated with the best survival, followed by SSM, and then NM (Clark et al. 1969; Søndergaard and Hou-Jensen 1977; Larsen and Grude 1978 A; Eldh et al. 1978; Balch et al. 1978; Drzewiecki et al. 1980; McGovern et al. 1979 and 1980; Esch et al. 1981).

It might be presumed that the different malignancy of LMM, SSM, and NM was basically due to their different cellular composition, so that the same prognosis was associated with melanomas of same cell type regardless the histological type of melanoma. As shown in Table 7 this was not so. For same cell type the best prognosis was correlatet with LMM, followed by SSM and then NM. However, also the cell type influenced prognosis, since in both SSM and NM the best prognosis was associated with the nevoid cell type, followed by the spindle cell type, and then the mixed and the epithelioid cell type (Table 7). In only LMM the cell type did not influence prognosis significantly.

Conclusions

1. The histological classification of primary cutaneous melanomas along the lines described by Clark et al. (1969) and McGovern et al. (1973) was readily applied to the vast majority of the melanomas.

2. SSM was the most prevalent type (65%), followed by NM (27%) and then LMM (4%). Only 4% of the melanomas were of unclassifiable type.

3. SSM arose more frequently from antecedent nevi, which were lifelong or of more than 5 years' duration (66%), than did NM (56%) and LMM (23%).

4. Microscopic examination showed benign nevus cells more frequently in SSM (11%) than in NM (5%) and LMM (4%).

5. The duration of symptoms was shortest for NM (<1 year: 83%) followed by SSM (<1 year: 74%), and longest for LMM (>3 years: 53%). The average tumor volume (corresponding to average tumor thickness) was about the same for LMM and SSM, but much greater for NM. Consequently the growth rate was greatest for NM, followed by SSM, and lowest for LMM.

6. More LMM (38%) had spindle cells as the dominant invasive tumor cell than had NM (7%) and SSM (4%).

7. LMM was almost exclusively seen on sun-exposed areas in elderly persons, whereas SSM and NM were found on both exposed and non-exposed areas in all ages after aldolescence, with a peak incidence at 45–54 years.

8. The 10-year survival rate was highest for LMM (79%), followed by SSM (69%), and then NM (46%).

The present study supported the basic principle of Clark's classification, that the 3 histological types represented distinctive entities of melanoma with different clinical, cellular, and behavioral characteristics. The classification is recommended for the histological reporting of primary cutaneous melanoma, as it is readily applied to the vast majority of melanomas and might be correlated with aetiologic differences (McGovern 1970; Kripke 1979; Ariel 1980).

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References

Ackerman AB (1980) Malignant melanoma. A unifying concept, Human Pathol 11:591–595

Ariel IM (1980) Theories regarding the cause of malignant melanoma. Surg Gynecol Obstet 150:907–917

Ariel IM (1982) Malignant melanoma of the trunk. A retrospective review of 1128 patients. Cancer 49:1070–1078

Balch CM, Murad TM, Soong S-J, Ingalls AL, Halpern NB, Maddox WA (1978) A multifactorial analysis of melanoma: Prognostic histopathological features comparing Clark's and Breslow's staging methods. Ann Surg 188:732–742

Bodenham DC (1968) A study of 650 observed malignant melanomas in the south-west region. Ann R Coll Surg Engl 43:218–239

Breslow A (1970) Thickness, cross-sectional areas and depth of invasion in the prognosis of cutaneous melanoma. Ann Surg 172:902–908

Clark WH (1967) A classification of malignant melanoma in man correlated with histogenesis and biologic behavior. In: Montagna W, Hu F (eds) Advances in biology of the skin, the pigmentary system. Pergamon Press Ltd., London, pp 621–647

Clark WH, From L, Bernardino EA, Mihm MC (1969) The histogenesis and biologic behavior of primary human malignant melanomas of the skin. Cancer Res 29:705–727

Clark WH, Heggeler B ten, Bretton R (1972) Electron microscope observations of human cutaneous melanomas correlated with their biologic behavior. In: McCarthy WH (ed) Melanoma and skin cancer. Proceedings of the International Cancer Conference. Blight VCN, Government Printer, Sydney, pp 121–141

Clark WH, Ainsworth AM, Bernardino EA, Yang C-H, Mihm MC, Reed RJ (1975) The developmental biology of primary human malignant melanomas. Sem Oncology 2:83–103

Clark WH, Folberg R, Ainsworth AM (1979) Tumor progression in primary human cutaneous

malignant melanomas. In: Clark WH, Goldman LI, Mastrangelo MJ (eds) Human malignant melanoma. Clinical oncology monographs. Grune & Stratton, New York, pp 15–31
Cochran AJ (1968) Histology and prognosis in malignant melanoma. J Pathol 97:459–468
Drzewiecki KT, Christensen HE, Ladefoged C, Poulsen H (1980) Clinical course of cutaneous malignant melanoma related to histopathological criteria of primary tumor. Scand J Plast Reconstr Surg 14:229–234
Elder DE, Ainsworth AM, Clark WH (1979) The surgical pathology of cutaneous malignant melanoma. In: Clark WH, Goldman LI, Mastrangelo MJ (eds) Human malignant melanoma. Clinical oncology monographs. Grune & Stratton, New York, pp 55–108
Elder DE, Jucovy PM, Clark WH (1982) Melanoma classification. A testable hypothesis, Am J Dermatopathol 4:443–445
Eldh J, Boeryd B, Peterson L-E (1978) Prognostic factors in cutaneous malignant melanoma in stage I. A clinical morphological and multivariate analysis. Scand J Plast Reconstr Surg 12:243–255
Esch EP van der, Cascinelli N, Preda F, Morabito A, Bufalino R (1981) Stage I melanoma of the skin: Evaluation of prognosis according to histologic characteristics. Cancer 48:1668–1673
Heenan PJ, Holman CDJ (1982) Nodular malignant melanoma: A distinct entity or a common end stage? Am J Dermatopathol 4:477–478
Kripke ML (1979) Speculations on the role of ultraviolet radiation in the development of malignant melanoma. J Nat Cancer Inst 63:541–548
Larsen TE (1978) The classification of primary cutaneous malignant melanoma. A prospective study of 60 cases using Clark's classification. Acta Path Microbiol Scand, Sect A 86:451–459
Larsen TE, Grude TH (1978A) A retrospective histological study of 669 cases of primary cutaneous malignant melanoma in clinical stage I. 1. Histological classification, sex and age of the patients, localization of tumour and prognosis. Acta Pathol Microbiol Scand, Sect A 86:437–450
Larsen TE, Grude TH (1978B) A retrospective histological study of 669 cases of primary cutaneous malignant melanoma in clinical stage I. 2. The relation of cell type, pigmentation, atypia, and mitotic count to histological type and prognosis. Acta Pathol Microbiol Scand, Sect A 86:513–522
Levene A (1980) On the histological diagnosis and prognosis of malignant melanoma. J Clin Pathol 33:101–124
McGovern VJ, Caldwell RA, Duncan CA, Finley-Jones LR, Hardy EG, Hicks JD, Little JH, Quinn RL (1967) Moles and malignant melanoma: Terminology and classification. Med J Aust 1:123–125
McGovern VJ (1970) The classification of melanoma and its relationship with prognosis. Pathology 2:85–98
McGovern VJ, Mihm MC, Bailly C, Booth JC, Clark WH, Cochran AJ, Hardy EG, Hicks JD, Levene A, Lewis MG, Little JG, Milton GW (1973) The classification of malignant melanoma and its histologic reporting. Cancer 32:1446–1457
McGovern VJ (1976) Malignant melanoma: Clinical and histological diagnosis. John Wiley & Sons, Sydney
McGovern VJ, Shaw HM, Milton GW, Farago GA (1979) Prognostic significance of the histological features of malignant melanoma. Histopathology 3:385–393
McGovern VJ, Shaw HM, Milton GW, Farago GA (1980) Is malignant melanoma arising in a Hutchinson's melanotic freckle a separate disease entity? Histopathology 4:235–242
Milton GW (1972) The diagnosis of malignant melanoma. In: McCarthy WH (ed) Melanoma and skin cancer. Procedings of the International Cancer Conference. Blight VCN, Government Printer, Sydney, pp 163–174
Olsen G (1966) The malignant melanoma of the skin. New theories based on a study of 500 cases. Thesis. Acta Chir Scand Suppl 365
Petersen NC, Bodenham DC, Lloyd OC (1962) Malignant melanomas of the skin. A study of the origin, development, aetiology, spread, treatment, and prognosis. Br J Plast Surg 15:49–94
Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, Mantel N, McPherson

K, Peto J, Smith PG (1977) Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II.Analysis and examples. Br J Cancer 35:1–39

Reed RJ (1976) Cutaneous malignant melanoma. In: New concepts in surgical pathology of the skin. John Wiley & Sons, New York, pp 73–96

Søndergaard K (1980) The intra-lesional variation of type, level of invasion, and tumour thickness of primary cutaneous malignant melanoma. 55 malignant melanomas studied by serial block technique. Acta Pathol Microbiol Scand, Sect A 88:269–274

Søndergaard K, Hou-Jensen K (1977) Histology and prognosis in cutaneous malignant melanoma (English summary) Ugeskr Læg 139:2993–2996

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