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# Malignant Melanoma of the Skin: Report of 341 Cases Treated during the Years 1929-1943

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# MALIGNANT MELANOMA OF THE SKIN[1]

## Report of 341 Cases treated during the Years 1929—1943

by

*Bengt Sylvén*

This paper will summarize the results of treatment obtained at the Radiumhemmet in cooperation with several Swedish surgical departments in patients with cutaneous malignant melanoma, admitted during a 15-year period from 1929 through 1943. Our results are gained by means of conservative surgery in combination with irradiation. This analysis was performed with a view to elucidating factors of importance and possible deficiencies in present principles of treatment in order to improve future methods. For this reason, data regarding the indications for palliative treatment by surgery and radiation as well as records of many peculiar cases have been omitted. Detailed clinical reviews by MIESCHER (45), MOIR *et al.* (47), PACK & LIVINGSTON, and others (1, 3, 4, 9, 34) cover all pertinent aspects. The report was limited to melanomas of the skin in order to avoid cases with regional gland stations inaccessible to clinical classification. The tables are for comparison kept close to those published by PACK, PERZIK & SCHARNAGEL (54), who reviewed 862 cases seen at the Memorial Hospital from 1917 to 1946. For previous reports from Radiumhemmet the readers are referred to a paper by SCHARNAGEL (61) on cutaneous melanomas treated between 1921 and 1930, and further the epibulbar melanomas have been dealt with by LARSSON (39).

Considering pathological and biological aspects, the heterogeneity of this group of tumours is regarded as an established fact (5, 16, 52). Present insufficiencies in histological diagnosis and classification also influence the clinical management of melanomas to a certain degree. All the same, the factors for proper treatment are defined by the pronounced tendency to early and wide-spread dissemination and by the high degree of radio-

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resistance, generally displayed by malignant melanomas. This will rule out clinical experimentation in early cases. Rational treatment must therefore be based on the eradication of the primary melanoma and its satellites without undue delay. It should further be recalled, that our very limited possibilities to determine the true extent of the disease necessitate more radical and wider excisions than are usually performed. More patients will evidently be salvaged by too wide excisions than by inadequate or repeated operations. We hope that in suitable cases excision and dissection »in continuity» for melanoma, as advocated by the Memorial Hospital Group (52—56), and further the »prophylactic» dissection of regional glands (1, 9, 25, 28, 33, 34, 45, 52—54, 66) will provide more cures than previously used methods have given.

Irradiation treatment by means of large or »hypermassive» dosage may give cures in selected early cases of primary melanoma (11, 12, 23, 24, 29, 38, 42, 43, 47, 51). However, this method involves considerable delay in time and heavy tissue and vascular reactions, which may favour tumour spread. For these and other reasons we consider it unjustified to take the responsibility for routine irradiation of primary melanomas in early stages, in particular when safer methods are available (cfr. 58). In advanced cases, irradiation treatment is on the other hand of palliative value, which will be mentioned below.

## Calculation of End Results and Classifications

Our series comprises a total of 341 cases during the 15-year period mentioned above. Treatment was refused in 50 cases due to advanced metastases and/or senility. The remaining 291 verified cases available for analysis were divided into one »indeterminate group» and another »determinate group» according to recent suggestions by MacDonald (41). All living patients' records were brought up to December 1948 by means of our follow-up system.

In order to facilitate comparison with other statistics the conventional clinical 5-year cure rates are stated in the main tabulation of results (Table IV). This results in cases developing metastases after a 5-year period of apparent health (»latent» metastases or »delayed metastatic growth») being reported as cured. Since the percentage of such latent metastases was found to be fairly large, a simultaneous report of what is called »end results up to 1948» is made. The latter figures are more correct from a biological point of view and will come closer to the actual course of malignant melanoma.

Due to high average age of our patients a fairly high incidence of intercurrent deaths was met with. A survey according to the principles of MacDonald will consequently entail a lower net five-year end result

than would actually be the case if corrections were made for such intercurrent deaths. In these particular cases, however, the reviewer has not been able to determine the cause of death in every patient under question, nor was it possible to exclude that patients had tumour remnants or silent metastases, and therefore it seemed unjustified to present corrected figures.

All patients have been classified in stages according to the extent of the tumour process at admission, as ascertained by clinical means including all available radiographic and laboratory methods. This clinical screening is naturally impaired by similar errors as are all others of the same type; unavoidable mistakes with reference to lymph node screening and blood-borne metastases are apparent. The original classification was kept without later reclassifications.

*Stage I.* Localized melanoma confined to the skin. Local recurrences and near-by deposits in cutaneous lymphatics are included.

*Stage II.* Cases with regional lymph node metastases confined to one gland station only.

*Stage III.* Metastatic involvement of two or more groups of glands, and cases with distant metastases evidencing generalized tumour process.

Histo-pathological reports of primary tumours and all operated metastases were available. Nevi with questionable malignancy are not included unless they have developed metastases later on. Tumours of doubtful nevogenic origin were discarded. Previous classifications in »melanocarcinoma» and »melanosarcoma» were impossible to maintain, and therefore we resort to the common term »malignant melanoma» until more correct distinctions can be made (cfr. ALLEN).

## Incidence of Melanoma

*Relative frequency.* — During this 15-year period a total number of 4,867 patients with skin epitheliomas applied for treatment at Radiumhemmet. The ratio of malignant melanoma to skin carcinoma was thus 7 : 100. This ratio was considerably higher in young age groups than in older ones. Detailed analysis with regard to age groups and patients' occupation was omitted (cfr. 59).

*Distribution.* — The regional distribution of malignant melanoma in this series is recorded in Table I, which shows the previously well known differences in distribution from that of skin epithelioma. The possible etiological significance of this fact has been repeatedly discussed (59) but no clear explanation has been reached. The distribution of malignant melanoma is also different from that of common pigmented nevi (5, 54).

*Sex.* — In this series 57 per cent were females and 43 per cent males. Females were in majority in most age groups (Table VII).

*Age.* — The age distribution chart (Fig. 1) reveals the highest incidence 37 and 43 per cent in the age groups between 40 to 90 years. The youngest patient was 17 months

at admission, and the oldest 91 years. The ratio of patients admitted to treatment and those not admitted is shown in Fig. 1.

**Table I**

*Distribution of 341 Cases of Malignant Melanoma according to Site of Lesion*

| Site | | Per cent |
|---|---|---|
| Lower Extremity | | 31.0 |
| Exclusive of feet | 14.3 | |
| Feet, exclusive of nails | 16.1 | |
| Ungual | 0.6 | |
| Head and Neck | | 33.6 |
| Trunk | | 26.3 |
| Upper Extremity | | 8.4 |
| Exclusive of hands | 4.1 | |
| Hands, exclusive of nails | 2.6 | |
| Ungual | 1.7 | |
| Scrotal | | 0.3 |
| Unknown primary site | | 0.3 |

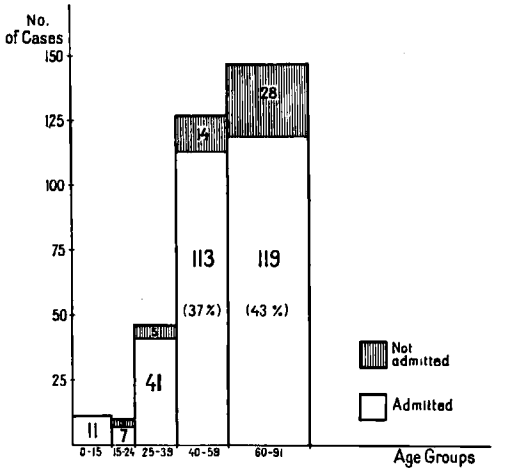



Fig. 1. Distribution of age groups in 341 patients with malignant melanoma of the skin.

## The Precursory Lesions

Of malignant melanomas of skin 40 to 65 per cent are commonly stated to originate in congenital or acquired pre-existing nevi. In elderly persons a small number of melanomas further arise in so-called »precancerous melanosis» (Lentigo maligna). The following data are of no value as far as the histogenesis of malignant melanoma is concerned (cfr. 5), and will only be mentioned for the purpose of the records.

**Table II**

*Percentage of Precursory Lesions in Malignant Melanoma of Skin*

| Colour of Primary Melanoma | Incidence of Pre-existing Congenital Nevus | | |
|---|---|---|---|
| | Feet | Hands | All other Sites |
| Black | 0 % | 0 % | 40 % |
| Brown | 50 | 50 | 50 |
| Blue or purple | 0 | 0 | 50 |
| Red, pink or skin-coloured | 11 % | 22 % | 23 % |

*Pre-existing pigmented nevi.* — With reference to the different colours and degrees of pigmentation in the present series of melanoma, a significant disparity was found in the incidence of previous »congenital» nevi, or nevi appearing during infancy. Patients with pigmented melanomas (black, brown, and blue or purple) related a history of a previous pigmented nevus since childhood in 40 to 50 per cent of all cases, except those of hands and feet (Table II). On the contrary a previous pigmented mole was only recorded in 23 per cent of patients with non-pigmented melanomas. Almost all melanomas (except part of the brown ones) appearing in hands and feet seem thus to be acquired (Table II). Our series further include one case of malignant melanoma arising in »bathing-trunk» nevi (Fig. 2).

These figures suggest that the innocent pigmented moles (intradermal nevi) can only be considered as precursors to part of the malignant melanomas. The majority seem to be acquired, and probably arise from epidermal cells (cfr. 5). This lends further emphasis to the possible rôle of extrinsic factors for the initiation of melanoma (36).

*Precancerous melanosis.* — The records include 13 cases (4.4 per cent) of melanoma preceded *in loco* by a

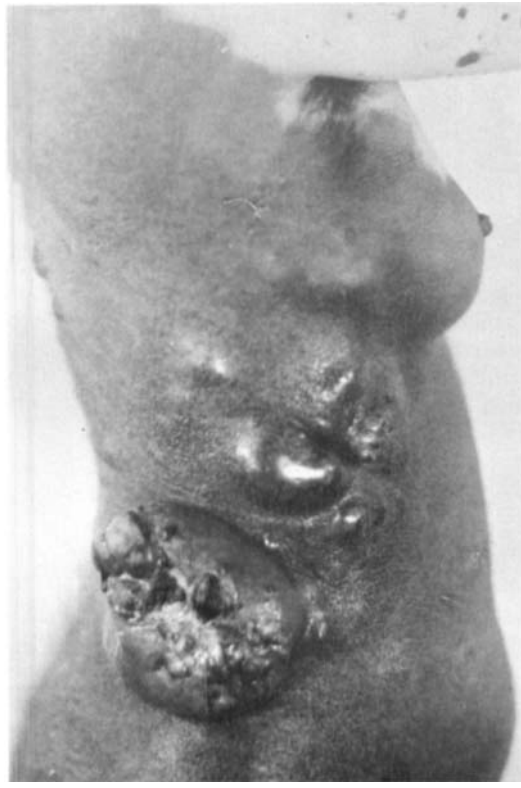


Fig. 2. Woman, aged 21, with multicentric rapidly growing giant melanomas in previous bathing-trunk nevus. At admission, 4 months after first sign of malignant change, the tumour process was generalized. (Case record No. 7001/1936.)

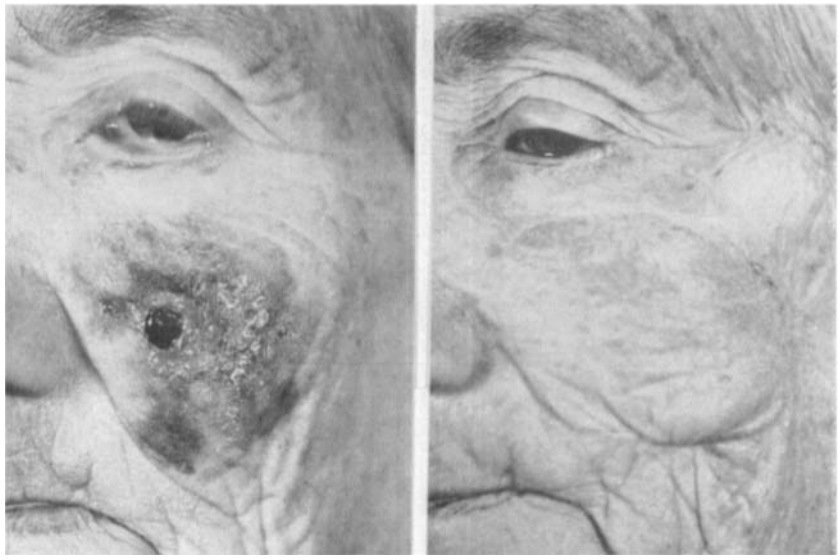


Fig. 3. Fig. 4.

Fig. 3. So-called »precancerous melanosis» with a richly pigmented melanoma at center. (Case record No. 9710/1940.)

Fig. 4. Following radical excision and plastic repair, this patient was living and well for 7 years.

typical precancerous melanosis with progressive growth (21, 44, 15). Most of these were located in the face. The induction time from the appearance of melanosis until established melanoma varied between 3 to 42 years (average induction time 11 years). Multiple foci of melanoma were repeatedly observed. The average age of these patients at admission was 70 years.

## Mode of Growth and Pigmentation

With regard to gross anatomy and mode of growth two main types of cutaneous melanomas may be distinguished. In most cases (97 per cent) small primary tumours showed marked tendency to infiltrative growth and early dissemination. The second type, characterized by large exophytic tumours with a chiefly expansive mode of growth and a more benign course, was registered in about 3 per cent of our cases.

A reversed ratio of similar melanoma types is found in animals. The more benign type has previously been recognized in a number of animals, such as horses (31, 62), dogs (7, 50), cats (45), mice (14, 30, 35, 65), and cattle (6), while the first mentioned infiltratively growing type occurs more seldom. Only a few verified melanomas have been obtained under long-continued applications of carcinogenic hydrocarbons to the skin of experimental animals. PASSEY (57) reported three exophytic melanomas in dogs; one was malignant. Following the application of benzpyrene SCHÜRCH (63) found one in-

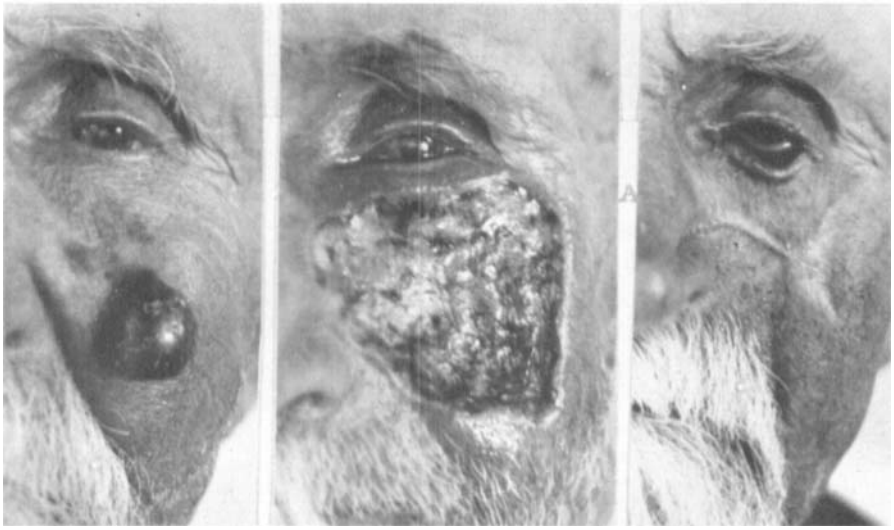


Fig. 5. Fig. 6. Fig. 7.

Fig. 5. Exophytic, mainly expansively growing, grape-like malignant melanoma in a man, aged 77. (Case record No. 5710/1934.)

Fig. 6. Patient's condition 10 days after a wide diathermy block dissection with subsequent superficial coagulation. Removed skin area 4 × 5 cm.

Fig. 7. Two months later, the wound was healed without grafting. Patient died 8 years later free from tumour.

filtrating and metastasizing melanoma in a rabbit. The commonly propagated laboratory melanomas of HARDING-PASSEY and CLOUDMAN differ in several respects from the behaviour of human malignant types (cfr. 5).

For the purpose of the records some attention was devoted to the capacity of pigment formation in primary melanomas, as evidenced by the colour of the primary tumours. The following percentage distribution was found in our determinate series of 251 patients:

| | |
|---|---|
| Black | 25 per cent |
| Brown | 28 » » |
| Blue or Purple | 13 » » |
| Red, Pink or Skin-coloured | 34 » » |

The ratio of melanomas poor in melanin is probably larger in this series than in previous ones (47). In untreated patients the red or skin-coloured melanomas were found to run a more rapid course than the pigmented ones (Table XIII).

## Routes of Dissemination

Part of this series was suitable for study of the relative frequency of the different modes of dissemination from the primary tumours (Table III), and thus some common clinical types may be distinguished (cfr. 52). The majority (54 per cent) developed early lymph node metastases diagnosed previous to or shortly after the treatment of the primary tumour. Latent gland metastases were registered in 7.5 per cent. Early generalization via the blood stream was further diagnosed in 28.5 per cent. This occurred either without simultaneous regional gland involvement (11.5 per cent) or with such involvement (17 per cent). Finally, a small number of cases (7.5 per cent) grew for years in the superficial lymphatics surrounding the primary locus (cfr. PACK & LIVINGSTON, p. 2078—2079).

Cases with early hematogenous spread from the primary focus constitute more than one fourth of our patients, which means that these were most likely already beyond help at admission to the hospital or shortly afterwards.

Regarding cases with regional lymph node involvement particular attention was focused on the possible time during which the tumour process was confined to the nodes. This is a question of great importance for the management of Stage I and II cases, and the figures to be presented show unfortunately that the lymph node barrier is broken very rapidly.

**Table III**

*Routes of Dissemination in 197 Cases of Malignant Melanoma of Skin*

| | | |
|---|---|---|
| Apparent Expansive Growth | | 2.5 % |
| Mainly Infiltrative Growth | | 97.5 % |
| Local lymphatic spread during several years, followed by fatal metastases | 7.5 % | |
| Early metastases to regional lymph nodes | 54 % | |
| Simultaneous lymph node metastases and hematogenous generalization | 17 % | |
| Early hematogenous spread without previous or simultaneous metastases to regional lymph glands | 11.5 % | |
| Late lymph node metastases and/or other »delayed metastatic growth» | [1] 7.5 % | |

[1] Metastases became evident after 5 to 16 years period of apparent health.

Melanoma cells are probably set free and carried by the blood a long time before clinical signs of distant metastases become evident. Previous authors have demonstrated tumour emboli in bone marrow punctures several months before the diagnosis of generalization was possible (17—20). This method may in future provide a more correct and earlier staging of melanoma patients, and further make mutilating operations unnecessary, as was discussed by DUBOIS-FERRIÈRE.

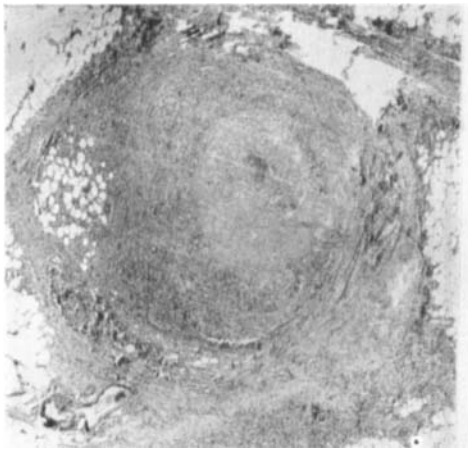


Fig. 8.

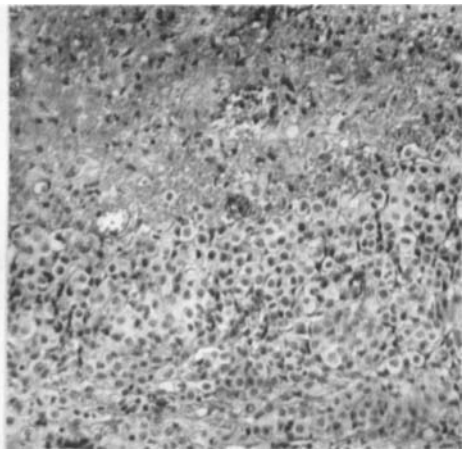


Fig. 9.

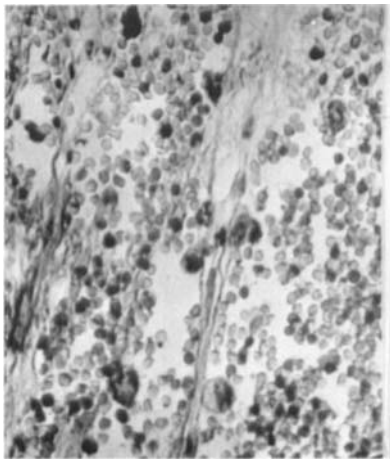


Fig. 10.

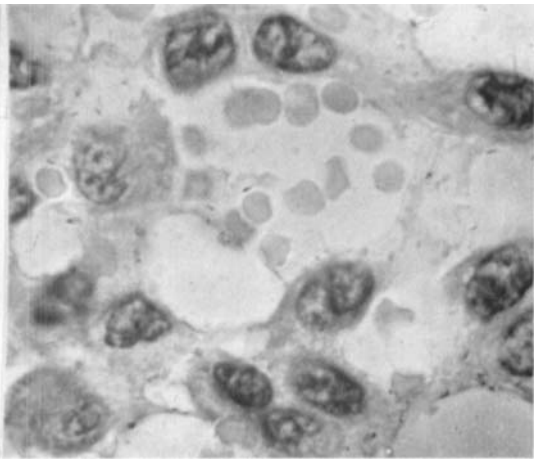


Fig. 11.

Fig. 8. The following slides show wide-spread involvement of blood vessels and lymphatic permeation in a case of recurrent non-pigmented melanoma of the calf. A medium sized superficial vein is invaded by tumour cells, growing into a central thrombus. (Case record No. 6904/1934.)

Fig. 9. Melanoma cells invading blood clot and freely capable to produce innumerable tumour cell emboli. (Slide No. 250/1936.)

Fig. 10. In a small subcutaneous focus isolated cells were found to grow among the blood corpuscles in a ruptured vessel.

Fig. 11. In such foci the tumour cells show pronounced loss of cohesion, which favours embolic spread, and illustrates the urgency of wide removal without undue delay (cfr. text).

## Differential Diagnosis

Regarding the importance of early clinical diagnosis it should be mentioned that in most pigmented melanomas (black, brown, blue, and purple) a correct diagnosis was made at the patients' first visit to the local physician. This was unfortunately not the case in patients with non-pigmented tumours (red, pink, or skin-coloured). The following examples will illustrate actual misinterpretations made by our staff.

Two brown melanomas were mistaken for pigment-forming squamous carcinoma and a senile wart, respectively, and were treated by radium implantation. One blue melanoma was taken for an angioma and electrocoagulated.

Eight cases with non-pigmented melanoma in the face were treated under the following provisional diagnoses: basal-cell carcinoma (3), squamous carcinoma (3), and angioma (2). Two melanomas located on the trunk got a first diagnosis of basal-cell carcinoma and angioma, respectively.

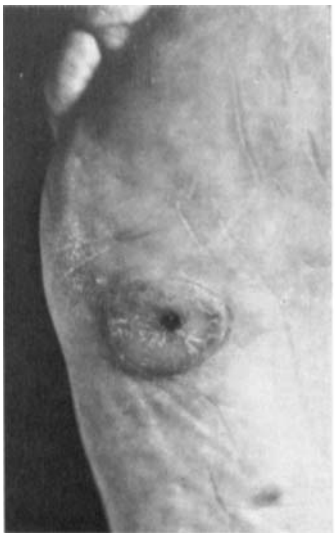


Fig. 12.

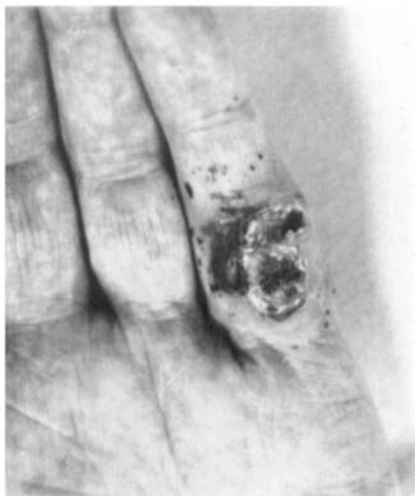
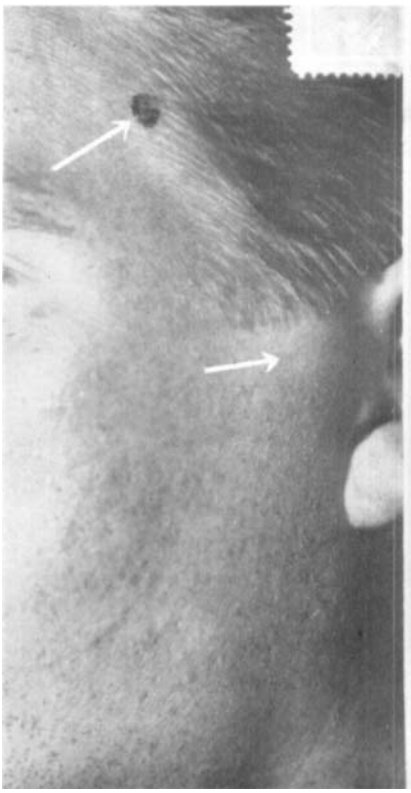


Fig. 13.

Fig. 12. This non-pigmented malignant melanoma was for one year interpreted as a plantar corn. Amputation was refused; the woman died of metastases 6 years after first symptom of tumour. (Case record No. 6954/1934.)

Fig. 13. In 1939 a woman aged 45, developed a small spot on her finger. This was mistreated by caustics and inadequate surgery. She entered this hospital in September 1941 with recurrence 15 × 18 mm in size, node metastases and pulmonar involvement. The primary was treated for palliative purposes with Roentgen irradiation (4,400 r in 8 days; 195 kV) without apparent effect. Length of survival from first symptom to death 30 months. (Case record No. 10947/1941.)



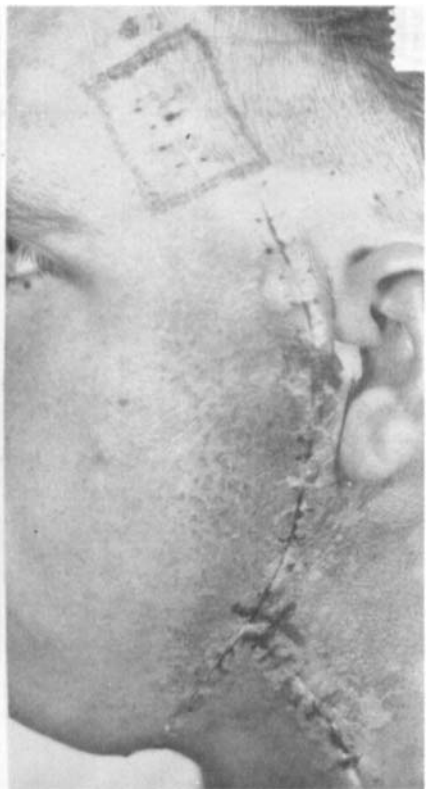


Fig. 14. Fig. 15.

Fig. 14. Previous to admission, a young man had a black nevus for 18 months, which was treated by incomplete electrodesiccation. This was followed by the development of preauricular and deep cervical nodes 9 months before admission. (Case record No. 6954/1934.)

Fig. 15. The nodes did not respond to preoperatively administered Roentgen irradiation (1,600 r). A radical extirpation and complete block dissection of cervical nodes was performed. Three months later distant metastases evidenced that generalization had actually occurred previous to operation. Length of survival from first sign of nevus to death 26 months, from the time of gland dissection only 8 months.

The non-pigmented melanomas on the feet and toes presented the greatest diagnostic difficulties; out of eight cases, 3 were misinterpreted as common plantar corns (Fig. 12), 1 was called a teleangiectatic granuloma, 1 a non-specific ulcer, another a diabetic gangrene, a seventh a chronic eczema, and the eighth a hemangioma.

Great harm was done by doctors, chiropodists, and beauticians, who treated early cases of malignant melanoma by freezing, caustics, and electric needling, whereby diagnosis and adequate therapy were delayed (Fig. 13—15).

## Principles of Treatment Applied in this Material

Due to a variety of circumstances beyond our control uniform therapy methods have neither been possible to apply in Stage I nor in Stage II patients (cfr. 61). In general it may be said, that the primary tumours have at this or other hospitals been subjected to local interventions either by clean surgery, or by electrosurgery. Depending upon the site of lesion, more or less wide block excisions were made which is considered as »restrictive» or conservative surgery (Fig. 3 & 4). Large excisions and/or mutilating operations were performed only in cases with recurrences or local secondary growths.

Diathermy block excisions included removal of the primary tumour, the surrounding skin area, all of the underlying fat tissue, and preferably also the deep fascial covering. Afterwards the wound was superficially coagulated with the diathermy current, and then left to granulate. In about 2—4 months the defect was replaced by soft scar tissue. In a few cases secondary skin-grafting was done. The results are illustrated in Fig. 6 & 7.

Patients with suspected or manifest lymph node involvement have caused considerable difficulty. Prophylactic gland dissection advocated by a number of previous authors has not been used. In Stage I cases with questionable regional nodes irradiation therapy in moderate dosage (1,400—2,000 r) was administered, and then the glands were closely watched. If the examination later on (Table X: after 1 to 19 months) indicated metastatic growth, dissection was performed. Patients admitted in Stage II were either operated at once and then subjected to postoperative irradiation (Roentgen or teleradium), or otherwise preoperative irradiation (1,600—2,800 r) was first given in order to facilitate the subsequent gland dissection (Fig. 14 & 15) in cases with debatable operability. Stage III patients were naturally referred to palliative treatment only, preferably by Roentgen irradiation. For additional treatment data the readers are referred to previous report (61).

The plans of treatment just outlined indicate that the primary melanomas were in general treated as surgical emergencies as early as 20 to 30 years ago. The regional gland deposits were, however, treated more or less like all other cancer metastases without realizing what delay in time could effect.

## Report and Evaluation of Results

High percentage cure rates were obtained in this material (Table IV) as compared with previous reports from other clinics (1, 3, 4, 9, 10, 13, 28, 37, 47, 54, 60); the conventional 5-year cure rate amounts to more than 34.6 per cent (uncorrected), and the late end result up to 1948 is 30.8 per cent (uncorrected). The over-all 5-year survival rate was 9.7

**Table IV**

*Tabulation of Main Results*[1]

| | | |
|---|---|---|
| Total number of patients applied for treatment | | 341 |
| Total number of patients admitted | | 291 |
| *Indeterminate group* | | |
| Dead within five years of other causes, probably without recurrence of melanoma | 28 | |
| Lost track of | 0 | |
| Total number of indeterminate results | | 28 |
| *Determinate group* | | |
| Total number | | 263 |

| | Conventional 5-year cure rates | End results at 1948 |
|---|---|---|
| *Failures* | | |
| Dead as a result of melanoma | 163 | 167 |
| Living with recurrent melanoma | 9 | 15 |
| Total number of failures in treatment | 172 | 182 |
| *Successful results* | | |
| Free from melanoma | 91 | 81 |
| Prepubertal group, all living | 11 | 11 |
| Adult group, living free from melanoma | 60 | 50 |
| Adult group, dead of other causes but free of symptoms more than five years after treatment | 20 | 20 |
| *Conventional net five-year end result* | 34.6 per cent | |
| *End result at 1948* | | 30.8 per cent |
| *Over-all end result at 1948* including all patients | | 23.7 per cent |

[1] Form according to Dr. ELEANOR J. MACDONALD.

per cent in the Memorial Hospital series of 595 cases (54), and is more than 26.7 per cent in ours. The analysis to be presented indicates (Table V & VI), that this high cure rate is due to the high percentage distribution of Stage I patients in our series. Our cure rate in Stage II patients (Table VI: 8.0 and 6.7 per cent) is on the same low level as that obtained in most other clinics.

This illustrates the inadequacy of reports only including end-results (41). For proper evaluation of methods and results, clinical staging is of prime importance. With reference to this particular material, we happen to know that the Memorial Hospital series include a larger percentage of advanced cases than our material does (54; and personal communication), and this renders the results incomparable.

It is further evident from Table VII, that the *prepubertal* (juvenile) *melanomas* do not behave like other malignant melanomas although their histology is indistinguishable from those occurring in later age groups.

**Table V**

*Distribution of Clinical Stages at Admission*

| | No. of patients | Percentage |
|---|---|---|
| Stage I | 188 | 55 |
| Stage II | 77 | 23 |
| Stage III[1] | 76 | 22 |

[1] Including 50 patients not admitted.

**Table VI**

*Cure Rates in Relation to Stage at Admission*

Only adult patients of Determinate Group are included.

| | Total No. of treated Patients | Conventional 5-Year Cure Rates in per cent | End Results in per cent up to 1948 |
|---|---|---|---|
| Stage I | 151 | 48.3 | 43.0 |
| Stage II | 75 | 8.0 | 6.7 |
| Stage III | 26 | 3.8 | 0 |

**Table VII**

*End Results at 1948 in 263 Cases of Melanoma in Relation to Age Groups*

| Age Period and Sex | Total No. of Cases | No. of Cured Cases | End Results in per cent at 1948 |
|---|---|---|---|
| Prepuberty | 11 | 11 | 100 |
| Puberty through 24 years: | | | |
| Females | 3 | 1 | 33 |
| Males | 4 | 3 | 75 |
| 25 through 39 years: | | | |
| Females | 26 | 9 | 34 |
| Males | 15 | 4 | 27 |
| 40 through 59 years: | | | |
| Females | 65 | 14 | 21 |
| Males | 45 | 10 | 22 |
| 60 years and over: | | | |
| Females | 52 | 17 | 33 |
| Males | 42 | 12 | 28 |

This corroborates previous statements (1, 5, 52, 54—56, 64) and calls for separation of the prepubertal melanomas so far clinical reports are concerned. A few actually metastasizing melanomas in children have been reported (49, 64).

**Table VIII**

*End Results at 1948 in 252 Cases of Malignant Melanoma of Skin in Relation to Primary Site of Tumour and Stage at Admission*

Prepubertal melanomas not included.

| | Stage | Total No. of Cases | No. of Cured Cases | Cure Rates in per cent at 1948 |
|---|---|---|---|---|
| *Lower extremity:* | | | | |
| Leg, exclusive of feet | I | 21 | 8 | 38 |
| | II | 11 | 1 | 9 |
| | III | 3 | 0 | — |
| Feet, exclusive of nails | I | 22 | 7 | 32 |
| | II | 11 | 0 | — |
| | III | 6 | 0 | — |
| Subungual | I | 2 | 0 | — |
| *Head* and *Neck* | I | 56 | 32 | 57 |
| | II | 23 | 0 | — |
| | III | 3 | 0 | — |
| *Trunk* | I | 34 | 10 | 29 |
| | II | 24 | 3 | 12 |
| | III | 11 | 0 | — |
| *Upper extremity:* | | | | |
| Arm, exclusive of hands | I | 7 | 3 | 42 |
| | II | 4 | 1 | 25 |
| | III | 2 | 0 | — |
| Hands, exclusive of nails | I | 9 | 4 | 44 |
| | II | 0 | 0 | — |
| | III | 1 | 0 | — |
| Subungual | I | 0 | 0 | — |
| | II | 2 | 0 | — |

No significant differences in cure rates can be claimed with reference to the various adult age groups (Table VII), nor are there any sex differences. The end results at 1948 in relation to primary site of melanoma are listed in Table VIII. In Stage I cases, a better prognosis was found for those involving the face and upper extremity (cfr. 1). A very poor prognosis indeed was obtained for most Stage II patients irrespective of site of primary lesion (Table VIII).

Before going into details it should thus be emphasized that the extent of the disease is above all the determining factor for the prognosis, and that our results are fair in Stage I patients, but poor in Stage II cases. This indicates that the methods so far applied by us until 1943 in the treatment of lymph node involvement are unsatisfactory.

*Analysis of Stage I patients.* — Only Stage I patients were suitable for evaluation of different methods used in the local eradication of pri-

**Table IX**

*Results of Treatment of Primary Tumour and Local Recurrences in 151 Stage I Patients*

| | Total No. of Cases | No. and Percentage of Patients living free of Symptoms at 1948 | No. and Percentage of postop. Local Recurrences | No. and Percentage of Lymph Node Metastases appearing after Operation | Hematogenous Spread shortly after Operation |
|---|---|---|---|---|---|
| Surgical excisions ..... | 88 | 40 (45 %) | 16 (18 %) | 37 (42 %) | 10 (11 %) |
| Electro-surgery acc. to Radiumhemmet's practice ..... | 53 | 21 (40 %) | 13 (24 %) | 26 (49 %) | 8 (15 %) |
| Irradiation followed by radical surgery ..... | 10 | 4 (40 %) | 2 (20 %) | 4 (40 %) | 2 (20 %) |

mary melanomas. As was mentioned previously, surgical and electrosurgical methods applied in our cases are regarded as conservative measures, which do not involve very wide excisions. The figures in Table IX indicate that similar results were obtained with both methods. The percentage of local recurrences was about the same after diathermy excisions, as performed at Radiumhemmet, than after clean surgery performed in this hospital or by other surgeons elsewhere. Neither was a significant difference found in the incidence of lymph node metastases following either method. The figures presented here cannot be said to favour any method *provided radical interventions are performed.*

Our series of local recurrences following non-radical operations is very variable as regards site of lesion, length of time between the first and second operations, appearance of metastases etc. It is therefore difficult to give a fair evaluation of the decrease in cure rate ascribable to the presence of local tumour remnants *per se.* It can only be stated that the cure rate is considerably diminished (cfr. 1). In Table IX a small number of cases is included, which were first treated by irradiation on an erroneous primary diagnosis, and then excised. The figures are given for comparison, and cures are ascribed to the subsequent surgical intervention.

A second point of extreme importance is the management of regional lymph node metastases appearing in Stage I patients after treatment of the primary melanomas. We would expect this group to show a better prognosis than those admitted to the hospital already in Stage II, and generally being in a more advanced state. Separate records were therefore prepared, and the first mentioned group is found in Table X. The final results are indeed very poor; only 5 patients are considered cured out of the whole number of 52 patients, or out of the 38 actually dissected patients (13 per cent). The figures in Table X suggest that our so-called »prophylactic» gland irradiation in its present form, as well as preopera-

**Table X**

*Results of Treatment in 52 Stage I Patients who Developed Regional Lymph Node Metastases after Admission*

| | Total No. of Cases | No. and Percentage of Cures up to 1948 | No. of Performed Gland Dissections | No. of Cases not operated | Delay in months between suspicion of metastases and time of operation (approx.) |
|---|---|---|---|---|---|
| Gland metastases following »prophylactic irradiation»; actual treatment direct surgery ... | 26 | 1 (3.8 %) | 16 | 10 | 1 to 19 |
| Operated cases only ..... | | 1 (6.2 %) | | | |
| Preoperative irradiation + subsequent gland dissection..... | 12 | 1 (8.3 %) | 12 | 0 | 1 to 7 |
| Gland dissection + subsequent postoperative irradiation .... | 10 | 3 (30 %) | 10 | 0 | 1 to 4 |
| Only Roentgen or teleradium irradiation ..... | 4 | 0 | 0 | — | — |

tively administered irradiation to such early node metastases is of questionable value. One of the main reasons for this seems to be that *both methods involve loss of time*, which means delay before gland dissections are performed (cfr. Table X). In any case, the cures obtained have to be ascribed to surgical intervention. Although the patients under question are not strictly comparable and in spite of the limited number of patients in different treatment groups, Table X indicates that more cures would probably be obtained when early gland dissection is performed. It is further a matter of argument if and when postoperative irradiation treatment to the gland regions should be given. This cannot be discussed with reference to the present material.

In a clinical material like this, it seems indeed impossible to evaluate so-called »prophylactic» gland irradiation with moderate or small doses. Following the radical excision of the primary melanoma, about one third of our Stage I patients will develop palpable nodes. This means that tumour cells must have reached the glands and remained undiagnosed since the time of the first operation. We know in this particular case, that irradiation treatment in its present state cannot kill melanoma cells deposited in lymph nodes, only a temporary suppression of growth can be effected depending upon the dosage given. From a scientific point of view, *this* type of »prophylactic» irradiation seems to be based on hypothetic considerations of questionable value. This and related problems were discussed more in detail by FORSSELL (27), EBENIUS (22) and others.

The final outcome in 151 Stage I cases is evidenced in Table XI. Out of 65 patients free of symptoms in 1948, 60 never developed any nodes. In the group with metastases to lymph nodes, only 5 were salvaged by the

**Table XI**

*Summary of Events in Our Stage I Patients (Determinate Group) up to 1948*

| | | |
|---|---|---|
| Living free of symptoms at 1948: 5—19 years after treatment of primary melanoma | | 65 |
| Never got lymph node or other metastases | 60 | |
| Got gland metastases operated | 5 | |
| Living with recurrences and/or metastases | | 13 |
| Dead as a result of melanoma | | 73 |
| Lymph node metastases and subsequent hematogenous spread | 47 | |
| Insidious hematogenous spread from primary or unknown focus | 21 | |
| Simultaneous lymph node metastases and hematogenous spread | 5 | |
| Total number of patients | | 151 |

**Table XII**

*End Results in Lymph Node Metastases Appearing in Stage II Patients*

| | Total No. of Cases | Living free of symptoms at 1948 | Living at 1948 with rec. and/or metastases | Dead from melanoma | Duration in months of palpable nodes before dissection (average) | Time from dissection until generalization in months (average) | No. of recurrences in scar and/or new metastases (incomplete dissections) | Average age of patients[1] |
|---|---|---|---|---|---|---|---|---|
| Surgery, alone, no irradiation | 3 | — | — | 3 | 1.6 | 4 | — | 55 |
| Gland dissection + postoperative irradiation | 25 | 1 | — | 24 | 3 | 12 | 14 | 55 |
| Preoperative roentgen + subsequent gland dissect. | 14 | 1 | 1 | 12 | 3 | 11 | 6 | 47 |
| Preoperative teleradium + subsequent gland dissect. | 11 | 3 | — | 8 | 3 | 10 | 3 | 52 |
| Radiation alone, no surgery | [2] 22 | — | — | 22 | — | [3] 8 | — | 54 |
| | 75 | 5 | 1 | 69 | — | — | — | — |

[1] Youngest patient 20 years, oldest 81 years.

[2] The nodes were in 21 patients most likely operable before irradiation was instituted, but 2 months later they were considered inoperable.

[3] Time from irradiation until generalization was evident. Patients in this group survived after irradiation from 4 months to maximum 4 years, average 15.6 months.

present treatment methods. Those who got insidious hematogenous spread (21 cases) could only have been salvaged by earlier diagnosis and treatment.

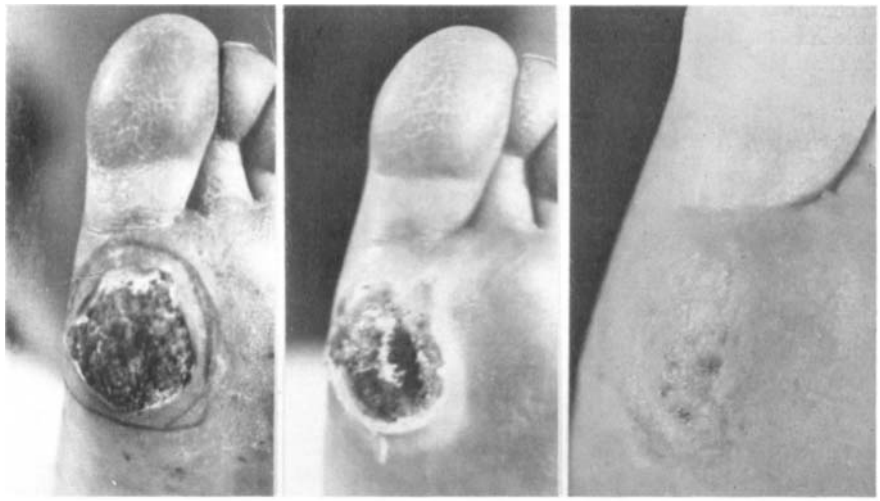


Fig. 16. Fig. 17. Fig. 18.

Fig. 16. At admission of a plantar malignant melanoma Stage I, the tumour was found to be non-pigmented with a papillomatous surface and measured $32 \times 35 \times 10$ mm. To a field $6 \times 7$ cm. in size we administered during 20 days a Roentgen dose of 4,700 r (100 to 180 kV). (Case record No. 6495/1934.)

Fig. 17. The melanoma had diminished considerably in size after 4 weeks.

Fig. 18. Two months after treatment, the ulcer was almost healed and no clinical signs of tumour were left. However, tumour remnants were verified by biopsy at this time, and later on in specimen obtained after amputation performed 4 months after radiation treatment. This case ran a fatal course 2 years after admission. Adequate surgery was delayed by irradiation.

*Analysis of Stage II patients.* — The variable structure of this group of cases warrants no detailed analysis regarding different treatment methods. Moreover, no representative number of patients only treated by surgery is included (Table XII) and consequently similar comparison as reported in Stage I patients cannot be made. Due to the fact, that many patients admitted in Stage II were in an advanced state, only part of the cases were operated upon (53 dissections in 75 patients). The more advanced gland involvement in Stage II excludes direct comparison and joint calculations with the early cases in Table X. It seems thus only justified to report, that the actual cure rate up to 1948 was 6.7 per cent (5 patients out of 75). The corresponding figure calculated on operated (selected) patients only was 9.4 per cent (5 patients out of 53). All cures are ascribable to surgical interventions.

For the purpose of the records, a comparison between early (Table X) and more advanced (Table XII) gland cases treated by dissection and subsequent postoperative irradiation may be made. In the early cases of gland involvement the cure rate was about

30 per cent, but fell down to 4 per cent when the more advanced, but still operable, cases in Table XII were considered. The latter figure is from a statistical point of view more correct than the former.

The considerations just mentioned illustrate the insufficiency in present plans for gland treatment, and indicate moreover that the lymph node barrier is in general broken through more rapidly than we have ever believed. This means that time is a very important factor for the successful management of malignant melanoma (cfr. 1), and loss of time should be avoided, here as well as in all other rapidly invading and early disseminating tumours.

*Analysis of Stage III patients.* — From the view point of curability these patients afford little interest and have to be referred to palliative measures. Untreated cases are, on the other hand, of interest for study of the length of survival, whereby the variable malignancy of melanoma will be illustrated.

## Length of Survival in Fatal Cases

Study of fatal cases (Table XIII) reveals that surgical and radiation treatment, although inadequate, will increase the length of patients' survival as calculated from the first symptom of melanoma (cfr. 48). In spite of very large standard deviations for the average values, and although corrections for normal death rates were omitted, this statement seems justified with reference to patients admitted in Stage I and II. As to the length of survival in untreated Stage III patients, including those who obtained insignificant palliative irradiation, the figures tend to

**Table XIII**

*Life Expectancy in Non-Cured Melanoma Patients*

Average duration in months from first symptom of melanoma to death in tumour as calculated from failures only. Comparison between treated and untreated (Stage III) patients.

| | | | |
|---|---|---|---|
| *Black* | treated | Stage I | 58 months |
| | » | II | 37 |
| | not treated | | 33 |
| *Brown* | treated | Stage I | 67 |
| | » | II | 27 |
| | not treated | | 17 |
| *Blue* or *purple* | treated | Stage I | 35 |
| | » | II | 35 |
| | not treated | | 14 |
| *Red, pink* or *skin-coloured* | treated | Stage I | 51 |
| | » | II | 31 |
| | not treated | | 12.8 months |

indicate a shorter survival period in non-pigmented melanomas than in the pigmented ones (Table XIII).

Considering possible growth accelerating factors most authors stress the rôle of trauma; however that may be, it would be difficult to gain support for such an opinion from our clinical material. On the other hand, the impression was gained that the tumour process is definitely accelerated by *pregnancy* (cfr. 5).

This series includes six women, who either observed their melanoma during pregnancy, or became pregnant during treatment. All ran a rapidly fatal course. One of these had been free of symptoms for 6 years, and then latent metastases became vitalized during pregnancy. As well as in some other human carcinomas, pregnancy is thus considered as a serious complicating and accelerating factor, which should be avoided. Only one woman, radically operated several years previously and free of symptoms, has survived child-bearing.

## Discussion

During the period under question we have been fortunate to receive a large number of early melanoma cases, and this explains our high cure rate in Stage I patients (Table VI) as well as the good end-results (Table IV). The analysis illustrates that the methods under question are on the whole satisfactory for local treatment of very early cases, but give poor results in dealing with lymph node involvement (Tables X—XII). It seems therefore mandatory to change those treatment methods in order to improve the cure rate. Before going into details, I want to stress that suggestions herein made are merely considered as presumptive plans, the effects of which cannot at present be substantiated by material from the Radiumhemmet.

It need hardly be emphasized that future plans must pay due consideration to the biological characteristics of the melanoma cells, above all to their capacity of *very rapid* penetration of vessels and lymph node barriers. This will at once rule out all time-consuming treatment methods. This implies further that in evaluating treatment methods we are not justified to compare results gained in melanoma with common slowly growing and invading carcinomas. If comparisons can be made they should be made with tumour types showing similar biological characteristics. *Time* seems thus to be an important factor. A sound principle of oncology says, that it is safer to be in advance of the tumour process than behind.

The primary melanomas should be treated as a *surgical emergency* and the widest possible block excision should be performed. Any method can be used — surgical or electrosurgical — provided the radical eradication of all tumour tissue is rapidly secured, including the removal of the deep subcutaneous lymphatic drainage. Radiological treatment is considered unsafe, and time-consuming, and will only give cures in selected early cases. In suitable cases classified as Stage I, no surgeon should desist from early amputation of fingers, toes, or the external ear. The

principles for wide dissection and management of subsequent defects belong in the field of surgery (cfr. PACK *et al.*).

With reference to our methods up to 1943 it seems advisable to leave the conservative excisions, which are only considered justified in very early cases. Due to present inability in determining the extent of lymphatic permeation it should be safer to apply wider dissections, and these are expected to diminish the risk of recurrences and metastases. How large the actual increase in cure rate would be in a material like ours is to date impossible to estimate.

The matter of dispute is what to do with the regional gland involvement appearing in Stage I patients. Present methods have salvaged 5 cases only in our series (Table XI). By means of so-called prophylactic gland dissection an additional number of patients would most likely have been living and well. In a series of Stage I cases devoid of clinical nodes, and yet subjected to preventive dissections, PACK & LIVINGSTON found minute metastatic foci, undetectable by common clinical methods, in *50 per cent.* This constitutes a strong argument in favour of preventive dissections before the appearance of palpable nodes. Conclusive reports concerning the actual gain in cure rate by adopting this method have so far not been published. In 1946, PACK, PERZIK & SCHARNAGEL (54) only stated a considerable increase in salvage in a small number of cases operated.

With reference to our stock of patients, prophylactic gland dissection would have implied unnecessary dissections in 60 patients during the 15-year period under question. An average of 4 patients a year would have been no extra burden to our co-operating surgical departments.

With a view to improvement of cure rate in Stage I melanomas *it seems thus advisable to join previous authors* (1, 9, 25, 28, 33, 34, 45, 52—54, 66) *in recommending prophylactic gland dissection in all suitable cases.*[1]

Before leaving the prophylactic gland dissection it should be emphasized that this method is not applicable to melanoma situated »*in the midline of the face or chest for which a bilateral neck dissection or a bilateral axillary dissection would have to be carried out*» (1). — From surgical and pathological points of view, prophylactic dissections seem, however, to be of doubtful value as regards melanomas of the distal part of the extremities, because part of the lymphatic drainage is passing into deep lymphatics, where melanoma cells might lodge. This might be more or less eliminated by the latest recommendations by PACK to perform the subsequent gland dissection a few weeks after the operation of the primary melanoma.

Turning to Stage II patients our results of treatment are very poor and even a small increase in cure rate would be acknowledged. Un-

[1] Confer the following recommendations by ACKERMAN & REGATO: »*When the tumor is located in an area from which the lymphatic drainage is predictable, a radical dissection of the anticipated metastatic node areas is mandatory*, in spite of the fact that the nodes may not appear clinically involved.» (1, p. 180.)

fortunately, possible improvement cannot be expected to be very large, because the filtering glands seem to be too rapidly passed by melanoma cells, as mentioned above. In the management of our material up to 1943, we have not paid sufficient regard to melanoma as essential emergency cases (Table XII). It would thus be possible to change our plan of gland treatment to immediate gland dissection and subsequent massive postoperative irradiation. In suitable locations, some not too advanced cases would most likely be salvaged by more radical surgery without undue delay: *earliest possible block dissection of both primary tumours and regional glands »in continuity»* according to PACK, SCHARNAGEL & MORFIT. If this should be done »in continuity» or as a two-step intervention depends upon both the site of the primary lesion and the routes for tumour emboli (1).

If the primary is located on the head, neck or trunk, the suggested operations leave very little to be desired so far radicality is concerned. Melanomas of the extremities will have to be treated by amputation (cfr. 52, 53, 55). These more radical interventions have to be tried and evaluated. They are in accord with the principles for the usual mastectomy for mammary carcinoma according to HALSTED (1894), and the method used for the eradication en bloc of rectal carcinoma (MILES), which methods have provided large increase in cure rate. Why should not similar good results be obtained in patients with malignant melanoma? — PACK stated in 1947 (55), that *by applying such wide local excisions of the primary melanomas plus regional gland dissection »in continuity», the cure rate was increased by 600 per cent* in comparison with the cure rate previously gained by conservative surgery in combination with radiation. A detailed report of end-results in melanoma is consequently expected from the Memorial Hospital.

To sum up, it seems to me advisable to concentrate most of our attention firstly to the treatment of *Stage I* patients by adopting (1) *W i d e r excision of primary melanoma*, and (2) *Routine preventive dissections of regional glands*, and further to apply (3) *e a r l i e r and m o r e r a d i c a l surgical interventions* to our *Stage II* patients. This program implies much attention and interest on the part of our colleagues in surgery. Concurrently, continued education of physicians and medical students will keep their mind open to the early diagnosis of melanoma and to the possibilities of radical treatment at our cancer centers.

## Conclusions

Present treatment results and pertinent biological characteristics of malignant melanoma, such as early and marked invasiveness, affinity to the vascular system, marked loss of cellular cohesion, and rapid per-

meation of lymph glands, converge to the view, that time is one of the most important factors for successful management of malignant melanoma. Current trends in oncologic surgery towards more active and radical methods are in keeping with this and seem to be justified. The results herein reported are based on conservative surgical and electrosurgical interventions in combination with radiotherapeutical measures, which methods are on the whole directed to treatment of clinically established lesions. Our interventions have thus until now been behind the tumour process. This fact is substantiated by the present poor prognosis recorded in patients with tumour spread beyond the primary focus.

In order to improve the curability it would be wise to join previous authors in adopting prophylactic surgical interventions to predictable regional glands in all Stage I patients, and further to adopt more radical surgical methods without any delay to manifest lymph nodes and other satellite lesions in Stage II patients. These suggestions conform with present principles for treatment of mammary and rectal carcinoma, and have, moreover, been reported by previous authors to give improved cure rates. Radiological treatment in its present state should for preoperative suppression of growth be directed to regional nodes with questionable operability, and is further of palliative value.

The previously known disparity in malignancy between prepubertal melanomas and those in adults was corroborated, and this suggests that melanoma cells are under hormonal influence, which is further supported by the pronounced increase in malignancy observed during pregnancy.

## SUMMARY

Out of 341 patients with cutaneous malignant melanomas 291 verified cases (85.3 per cent) were admitted to treatment at the Radiumhemmet during a 15-year period from 1929 through 1943. Thanks to our close follow-up service complete records brought up to December 1948 were available for analysis. In spite of its limitations, clinical staging with reference to the extent of disease at admission is considered of prime importance for the evaluation of results. Data regarding the incidence, distribution, precursory lesions, modes of growth, and differential diagnosis, etc. have been cursorily mentioned. Present treatment methods characterized by conservative surgical interventions partly in combination with radiological treatment have in this material provided the following uncorrected cure rates: Net five-year cure rate (conventional) 34.6 per cent; End result at 1948 in determinate group 30.8 per cent; Over-all end result at 1948 23.7 per cent.

The opinion is forwarded that more patients would probably be salvaged by wider and earlier surgical intervention, and in particular by prophylactic gland dissection in Stage I patients.

## ZUSAMMENFASSUNG

Von 341 Kranken mit malignen Hautmelanomen wurden 291 verifiierte Fälle (85.3 %) in der fünfzehnjährigen Zeitspanne 1929—1943 in der Radiumklinik behandelt. Dank unseres genauen Nachuntersuchungssystems lagen vollständige Berichte bis Dezember

1948 zur Analyse vor. Trotz ihrer Begrenzungen hält Verf. die klinische Einteilung nach der Ausdehnung der Krankheit bei der Aufnahme für sehr bedeutungsvoll für die Berechnung der Ergebnisse. Angaben über die Verteilung der Häufigkeit, voraufgehende Erscheinungen, Wachstumsarten, Differentialdiagnose usw. werden kurz erwähnt. Die heutigen Behandlungsmethoden, die sich durch konservative chirurgische Eingriffe, teilweise mit Strahlenbehandlung kombiniert, auszeichnen, haben in diesem Material folgende unkorrigierte Heilungszahlen ergeben: Reine fünfjährige Heilungszahl 34.6 %; Endergebnis 1948 in bestimmter Gruppe 30.8 %; gesamtes Endergebnis 1948 23.7 %.

Es wird die Ansicht ausgesprochen, dass durch weitgehenderes und früheres chirurgisches Eingreifen und ganz besonders durch prophylaktische Ausschälung der Drüsen bei Kranken im I. Stadium wahrscheinlich mehr Patienten gerettet werden könnten.

## RÉSUMÉ

Sur 341 malades atteints de mélanomes malins de la peau 291 (85.3 %), dont le cas fut vérifié, ont été admis au Radiumhemmet pour traitement, pendant la période de 15 années allant de 1929 à 1943 inclusivement. Grâce à notre excellent service de contrôle posthospitalier des observations complètes, tenues à jour jusqu'à décembre 1948, étaient disponibles pour l'analyse du matériel. En dépit de ses imperfections, le système de la répartition en stades cliniques d'après l'étendue de l'affection lors de l'hospitalisation est considéré comme étant d'importance primordiale pour l'évaluation des résultats. Les données concernant la fréquence et la distribution des tumeurs, les lésions préexistantes, les modalités de l'accroissement, le diagnostic différentiel, etc., ont été mentionnées en passant. Les méthodes actuelles de traitement, caractérisées par des interventions chirurgicales conservatrices partiellement combinées avec la radiothérapie, ont dans ce matériel donné le pourcentage — non corrigé — que voici de guérisons: pourcentage net de guérisons après cinq ans (conventionnel), 34.6 %; résultat final en 1948 par groupe déterminé, 30.8 %; résultat final général en 1948, 23.7 %.

L'opinion est émise qu'on sauverait probablement davantage de malades par une intervention chirurgicale plus étendue et plus précoce, en particulier par la dissection prophylactique des ganglions chez les sujets du stade I.

## LITERATURE

1. Ackerman, L. V. & del Regato, J. A.: »Malignant Melanomas of the Skin» in Cancer. C. V. Mosby Co., St. Louis, p. 169, 1947.
2. Adair, F. E. & Pack, G. T.: Bull. Assoc. franç. p. l'étude du cancer 19: 549, 1930.
3. Adair, F. E.: Surg. Gynec. & Obst. 62: 406, 1936.
4. Affleck, D. H.: Am. J. Cancer 27: 120, 1936.
5. Allen, A. C.: Cancer 2: 28, 1949.
6. Anonym: J. Am. Vet. M. A. 105: 30, 1944. (Ref. in Cancer Research 6: 332, 1946.)
7. Auler, H. & Wernicke: Ztschr. f. Krebsforsch. 35: 1, 1932.
8. Ball, H. A.: Cancer Research 6: 134, 1946.
9. Bickel, W. H., Meyerding, H. W. & Broders, A. C.: Surg. Gynec. & Obst. 76: 570, 1943.
10. Bloodgood, J. C.: J. A. M. A. 79: 576, 1922.
11. Chaoul, H. & Greineder, K.: Strahlentherapie 56: 40, 1936.
12. Chaoul, H.: Die Nahbestrahlung. Georg Thieme. Leipzig, p. 131, 1943.
13. de Cholnoky, T.: Ann. Surg. 113: 392, 1941.

14. CLOUDMAN, A. M.: »Spontaneous Neoplasms in Mice» in Biology of the Laboratory Mouse. The Blakiston Co., Philadelphia, p. 168, 1941.
15. CORSI, H.: Proc. Roy. Soc. Med. 32: 261, 1939.
16. DAWSON, J. W.: Edinburgh M. J. 32: 501, 1925.
17. DICKER, S. & DUBOIS-FERRIÈRE, H.: Rev. méd. Suisse rom. 62: 820, 1942.
18. DUBOIS-FERRIÈRE, H.: Praxis 34: 353, 1945.
19. —: Rev. méd. Suisse rom. 66: 256, 1946.
20. —: Helvet. med. acta 13: 319, 1946.
21. DUBREUILH, W.: Ann. de Dermat. H. III: 129, 1912.
22. EBENIUS, B.: Cancer of the Lip. Acta Radiol. Suppl. 48, 1943. P. A. Norstedt & Söner, Stockholm.
23. ELLIS, F.: Brit. J. Radiol. 12: 327, 1939.
24. EVANS, W. A. & LEUCUTIA, T.: Am. J. Roentgenol. 26: 236, 1931.
25. EVE: The Practitioner, 1903 (cited by Handley).
26. EWING, J.: Brit. M. J. 2: 852, 1930.
27. FORSSELL, G.: On the Permanency of Radiological Healing in Malignant Tumors. Acta Radiol. Suppl. 2, 1928. P. A. Norstedt & Söner, Stockholm.
28. GLEAVE, H. H.: Lancet 2: 658, 1929.
29. GREINEDER, K. & NEUMANN, W.: Strahlentherapie 66: 89, 1939.
30. HAALAND, M.: 4th Scient. Rep. Imp. Cancer Research Fund, p. 69. 1908.
31. HADWEN, S.: Canadian M. A. J. 25: 519, 1931. (Ref. in Am. J. Cancer 16: 1281, 1932.)
32. HALSTED, W. S.: Ann. Surg. 20: 497, 1894.
33. HANDLEY, S. W.: Lancet 27: 927, 1907.
34. —: Lancet 1: 1401, 1935.
35. HARDING, H. E. & PASSEY, R. D.: J. Path. & Bact. 33: 417, 1930.
36. HEWER, T. F.: J. Path. & Bact. 41: 472, 1935.
37. HINTZE, A.: Arch. f. klin. Chir. 183: 55, 1935.
38. HULTBERG, S.: Undersuchung über die Röntgennahbestrahlung. Acta Radiol. Suppl. 54: 142, 1943. P. A. Norstedt & Söner. Stockholm.
39. LARSSON, H.: Acta Radiol. 27: 358, 1946.
40. LEE, F. C.: S. Clin. North. America 16: 1439, 1936.
41. MACDONALD, E. J.: Am. J. Roentgenol. 60: 832, 1948.
42. MCEUEN, H. B.: Radiology 14: 587, 1930.
43. MIESCHER, G.: Schweiz. med. Wchnschr. 7: 788, 1926.
44. —: Virch. Arch. 264: 86, 1927.
45. —: »Melanom» in Handb. d. Haut- u. Geschlechtskr. von J. Jadassohn, Berlin. XII: 3: II, p. 1005, 1933.
46. MILES, W. E.: Cancer of the Rectum. Harrison & Sons, London, 1926.
47. MOIR, P. J., DAWSON, E. K., TOD, M. C., BONSER, G. M., WILLIAMS, I. G. & ELLIS, F.: Brit. J. Radiol. 19: 217, 1946.
48. NATHANSON, I. T. & WELCH, C. E.: Am. J. Cancer 31: 598, 1937.
49. NOWKIRISCHKY, A. D.: Klin. Mbl. Augenheilk. 94: 521, 1935.
50. OTTOSEN, H. E.: Skand. Vet. Tidskr. 37: 207, 1947 (with an English summary).
51. OWEN, A. K.: Am. J. Roentgenol. 11: 335, 1924.
52. PACK, G. T. & LIVINGSTON, E. M.: »The Treatment of Pigmented Nevi and Melanomas» in Treatment of Cancer and Allied Diseases, Paul B. Hoeber, Inc. New York. III: 2071, 1940.
53. PACK, G. T., SCHARNAGEL, I. & MORFIT, M.: Surgery 17: 849, 1945.
54. PACK, G. T., PERZIK, S. L. & SCHARNAGEL, I. M.: California Med. 66: 283, 1947.
55. PACK, G. T.: South. Med. J. 40: 832, 1947.
56. —: Surg. Gynec. & Obst. 86: 374, 1948.

57. PASSEY, R. D.: J. Path. & Bact. 47: 349, 1938.
58. PATERSON, R.: The Treatment of Malignant Disease by Radium and X-rays. Edward Arnold & Co. London, p. 195, 1948.
59. PELLER, S.: Cancer Research 1: 538, 1941.
60. ROUSSY, G., HUGUENIN, R. & SARACINO, R.: Presse méd. 50: 193, 1942.
61. SCHARNAGEL, I. M.: Acta Radiol. 14: 473, 1933.
62. SCHOCH, A.: Dermatologica 88: 350, 1943.
63. SCHÜRCH, O.: Deutsche Ztschr. f. Chir. 252: 277, 1939.
64. SPITZ, S.: Am. J. Path. 24: 591, 1948.
65. STRONG, L. C.: J. Cancer Research 12: 208, 1928.
66. WEBSTER, J. P., STEVENSON, T. W. & STOUT, A. P.: S. Clin. North America 24: 319, 1944.
67. WERNER, R.: »Carcinom und Sarkome» in Lehrbuch d. Strahlentherapie, Urban & Schwarzenberg, Berlin, II: 249, 1925.
68. WILBUR, D. L. & HARTMAN, H. R.: Ann. int. Med. (Am.) 5: 201, 1931.