Prognostic Factors in Cutaneous Melanoma of the Head and Neck

Andrew G. Huvos, MD, Valerie Miké, PhD, Michael J. Donnellan, MB, BS, FRACS, Thomas Seemayer, MD and Elliot W. Strong, MD, FACS

The division of cutaneous malignant melanomas into nodular melanoma, malignant melanoma arising in Hutchinson's melanotic freckle and superficial spreading melanoma has, in many studies, indicated its usefulness for assessing prognosis. The depth of dermal invasion was also found to be an important prognostic factor. The present retrospective study of 119 patients, seen at Memorial Sloan-Kettering Cancer Center from 1947 to 1964, with cutaneous malignant melanoma of the head and neck area examines the above three types of melanoma as well as the depth of dermal invasion. The clinical and pathologic features and course of the disease in these patients were studied by means of a comprehensive statistical analysis. There was significant correlation between the depth of invasion and type of malignant melanoma, with the nodular type being the most deeply penetrating and melanoma arising in Hutchinson's melanotic freckle the most superficial ($P < .01$). The ten-year actuarial survival rates for clinical stage I patients when grouped according to dermal level of penetration were level II, 86%, vs level V, 44% ($P < .01$); levels III and IV were 60% and 57%, respectively. Correlations of importance were noted between ulceration and depth of dermal penetration, cellular pigment production and clinical pigmentation, as well as size of the primary lesion and depth of dermal invasion. It is suggested that future large-scale prospective studies include these useful parameters (Am J Pathol 71:33–48, 1973).

> One of the great advantages inherent in the concentrated review of a large number of histologic lesions is that, by such concentration, there is provided a sharper perspective for conclusions regarding their histologic details than by an equivalent experience diluted over a number of years.—A. C. Allen

RECENT STUDIES which have assessed the prognosis of patients with cutaneous malignant melanoma drew attention to a number of reliable criteria, including depth of invasion of the tumor and histologic type of melanoma (nodular melanoma, melanoma arising in Hutchinson's melanotic freckle and superficial spreading melanoma)

From the Departments of Pathology and Clinical Statistics, and the Head and Neck Service of the Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY.

Presented in part at the First Joint Meeting of the James Ewing Society, the American Radium Society and the Society of Head and Neck Surgeons, Boca Raton, Fla, May 1972.

Accepted for publication Dec 5, 1972.

Address reprint requests to Dr. Andrew G. Huvos, Memorial Hospital, 444 East 68th St, New York, NY 10021.

that seemed to affect the outcome of the disease.[1-9] Justifiable criticism could be leveled against such "research" studies on the basis of the lack of uniform conditions for tissue collection and processing, and the great expense of serial tissue sections which are unlikely to find application in a "routine" tissue laboratory. One of the reasons we undertook this retrospective study was to reconfirm, modify or reject these findings of previous studies in a Cancer Center which has treated large numbers of patients with malignant melanoma of the skin, employing no special studies to evaluate the depth of invasion of the dermis and the type of malignant melanoma occurring in the skin of the head and neck area.

Materials and Methods

The clinical records were obtained for 221 patients with the diagnosis of cutaneous malignant melanoma of the head and neck area established between January 1947 and December 1964 at Memorial Sloan-Kettering Cancer Center. Before clinical review, an intensive effort was made to obtain the histologic sections of the primary lesion from which the diagnosis had been made. In some instances this was not feasible, as tissue at other hospitals had been discarded, or the histologic sections were technically inadequate for establishing the presence and/or the depth of dermal invasion or the type of melanoma present. Excluded from this study were cases in which the primary lesion spontaneously regressed, or the original melanotic lesion was removed by fulguration or electrodesiccation and so no histologic material was available for study. The majority of cases were excluded because no specimens were obtained from the original excision. We based this clinicopathologic study on material available from 119 patients.

Two pathologists independently designated the primary cutaneous lesions as nodular melanoma, melanoma arising in Hutchinson's melanotic freckle or superficial spreading melanoma, as described by Clark *et al* [1,2] and McGovern.[7] In addition, the depth and extent of dermal invasion were established according to the following criteria:

Level I: The tumor is intraepidermal with intact basement membrane (noninvasive melanoma *in situ*).

Level II: The lesion extends only into the upper papillary dermis (papillary dermal level).

Level III: The tumor invades into deep papillary dermis and impinges on the interface between papillary and reticular dermis (papillary-reticular layer interface).

Level IV: The tumor extends into the reticular dermis (reticular-dermal level).

Level V: The tumor reaches into the subcutaneous adipose tissue (subcutaneous fat level).

The clinical information recorded for each patient included age, sex, duration of changes in the primary lesion prior to diagnosis, site of primary lesion, clinical stage of disease, extent of pigmentation, the presence of ulceration, tumor satellite formation, mode of treatment, time to last follow-up since diagnosis of primary lesion and status at the time of last follow-up. The histologic characteristics examined included, of course, the type of melanoma and depth of dermal

penetration. Also studied were the cell type of the primary lesion, cellular pigment production, the presence and extent of lymphocytic reaction in the primary lesion, mitotic rate and thickness of the lesion.

A comprehensive statistical analysis was carried out on the available data. The effect of the major characteristics on prognosis was examined by means of the life table method.[10] Pairs of the resulting actuarial survival curves were compared for a statistically significant difference by application of the Wilcoxon-Gehan test.[11] The relationship between variables was studied by means of contingency tables. All *P*-values reported below refer to two-sided tests.

The classic histologic descriptions of the three types of malignant melanoma are as follows:

Nodular malignant melanoma arises *de novo* from the unblemished skin. It is characterized by a fully invasive tumor without associated melanotic freckle or superficial spreading melanoma (no peripheral epidermal spread) (Figure 1). The invasive portion of the lesion may have epithelioid, spindle or mixed cellular growth characteristics (Figures 2 and 3).[12–20]

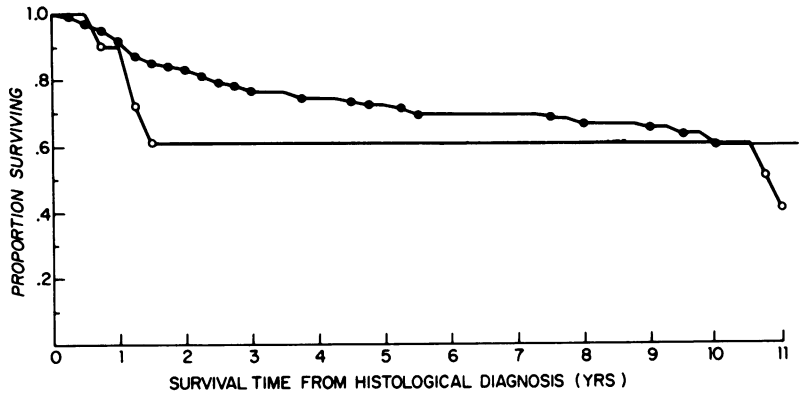
Malignant melanoma arising in Hutchinson's melanotic freckle (lentigo maligna melanoma) is microscopically characterized by an excessive proliferation of melanocytes, predominantly involving the basal layer of the epidermis with some extension into the midepidermis lateral to the invasive portion (intraepithelial component). These melanocytes may appear singly or in nests. The most characteristic feature of these melanocytic cells is their marked cellular pleomorphism. The admixture of pleomorphic and normal melanocytes is a singularly useful feature in distinguishing this lesion from a junctional nevus. Upon penetration of the basement membrane the invasive portion of the lesion is usually sparsely pigmented and is often composed of spindle cells. Occasionally a mixed epithelioid and spindle cell growth pattern is present (Figures 4 and 5).[2,3,5,9,21]

Superficial spreading melanoma (premalignant melanosis, Pagetoid melanoma) features a diffuse, adjacent, intraepidermal infiltration by large, strikingly uniform melanocytes with a distinct and peculiar resemblance to Paget-like cells. These abnormally large cells which vary little in size permit a clear distinction from Hutchinson's melanotic freckle. The dermal invasive portion of the lesion is composed of similarly large epithelioid cells with no spindle shaped cell variants (Figures 6, 7 and 8).[1,2,7,21,22]

Results

Our major findings are summarized in this section. We are aware that in some instances a real difference between groups may not have been detected due to the relatively small sample sizes involved. We found it convenient to list our results under the separate headings of "Positive Findings" and "Other Features Examined" (negative findings); because of the above consideration, we refrained from unqualified use of the term "negative."

Whenever a characteristic was studied for its effect on prognosis, only the 104 clinical stage I patients for whom the disease was localized at the time of diagnosis were included in the analysis. There were 13 patients in clinical stage II and 2 in clinical stage III. The actuarial survival curves for stage I and II patients are shown in Textfigure 1. For stage I patients the 5-year survival rate was 72%, and the



TEXT-FIG 1—Actuarial survival curves of patients by stage of disease. (Stage I, N = 104, *solid circles;* stage II, N = 13, *open circles*). There were only 2 patients in stage III.

10-year survival rate 60%. The number of stage II patients was too small for any definitive conclusions, but it is interesting to note that even among these patients, there were 4 long-term survivors (20 or more years).

The distribution of patients by type of melanoma and site of primary lesion is shown in Table 1.

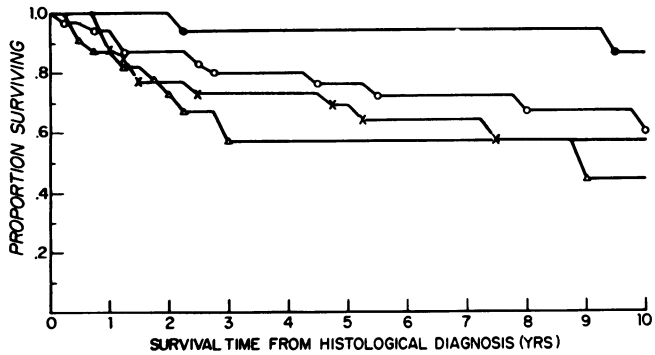
Positive Findings

Level of Dermal Invasion and Prognosis

A statistically significant relationship was found between the level of dermal invasion of the primary lesion and prognosis. The survival curves for levels II to V (clinical stage I) are shown in Text-figure 2; there were no level I lesions in our material. Level II was significantly different from levels III, IV and V. The 5-year actuarial survival rates for levels of invasion II, III, IV and V were 94, 76, 69 and 57%, respectively. The corresponding 10-year rates were 86, 60, 57 and 44%.

Table 1—Site and Type of Primary Lesion

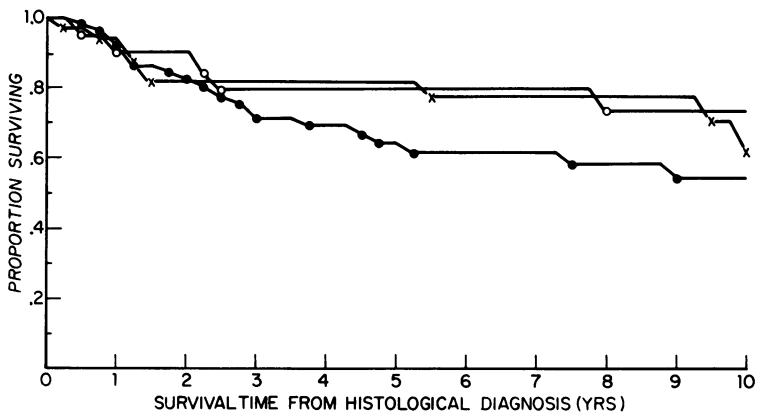
Site	Nodular melanoma	Melanoma arising in Hutchinson's melanotic freckle	Superficial spreading melanoma	Total
Scalp	16	1	12	29
Face	37	18	15	70
Neck	6	4	10	20
Total	59	23	37	119



TEXT-FIG 2—Actuarial survival curves according to the dermal level of invasion in clinical stage I patients (all three types of melanoma) (Level of invasion: II, N = 19, *solid circles;* III, N = 32, *open circles;* IV, N = 26, *X;* V, N = 23, *open triangles;* not known, N = 4; total = 104. II vs III: $P < .06$; II vs IV: $P < .03$; II vs V: $P < .01$; III vs V: $P < .09$).

Type of Melanoma and Level of Invasion

The survival curves for the three types of malignant melanoma are shown in Text-figure 3. Patients with nodular melanoma had a lower rate of long-term survival, but these curves were not significantly different from each other. A significant relationship was noted, however, between the type of melanoma and the depth of dermal invasion (Table 2; $P < .01$). Nodular melanoma was more frequently deeply invasive than the other two types of lesions. Melanoma



TEXT-FIG 3—Actuarial survival curves of the three types of melanoma in clinical stage I patients (Nodular melanoma, *solid circles;* melanoma arising in Hutchinson's melanotic freckle, *open circles;* superficial spreading melanoma, *X*).

Table 2—Correlation Between Level of Invasion and Type of Melanoma

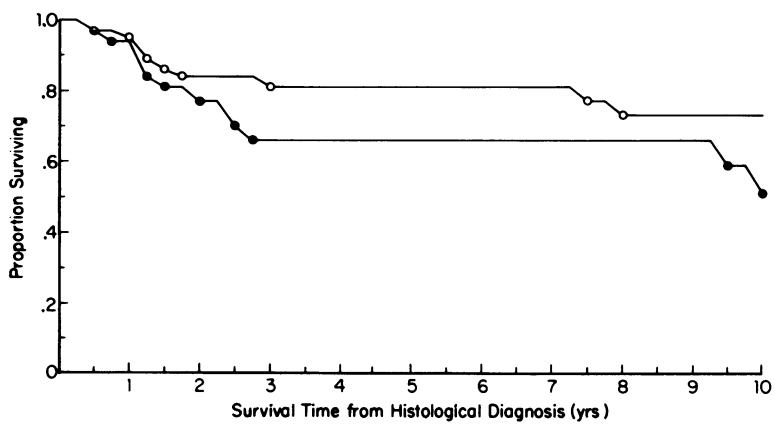
Level	Nodular melanoma	Melanoma arising in Hutchinson's melanotic freckle	Superficial spreading melanoma	Total
II	2	13	9	24
III	10	6	19	35
IV	19	3	7	29
V	21	1	2	24
Unknown	7	0	0	7

$P < .01$

arising in Hutchinson's melanotic freckle infiltrated in the most superficial manner, and superficial spreading melanoma occupied a midposition with regard to the depth of invasion.

Ulceration and Level of Invasion

Information concerning ulceration of the primary lesion was available for 79 patients, 72 of these being in clinical stage I. The patients with ulcerated lesions had a lower survival rate than patients with intact lesions (Text-figure 4), although the difference was not statistically significant. A significant correlation was observed, however, between ulceration and level of invasion (Table 3; $P < .02$). The percent of ulcerated lesions for levels II to V was 13, 44, 55 and 59%, respectively.



TEXT-FIG 4—The effect of lesional ulceration on survival in clinical stage I patients (Ulceration, N = 32, *solid circles;* no ulceration, N = 40, *open circles;* total = 72).

Table 3—Correlation Between Ulceration and Level of Invasion

Level	Ulcerated	Not ulcerated	Total	Percent ulcerated
II	2	13	15	13
III	11	14	25	44
IV	12	10	22	55
V	10	7	17	59
Total	35	44	79	44

$P < .02$

Size of Lesion and Level of Invasion

Microscopic examination of the primary lesion with exact measurement of the diameter of the invasive portion revealed a correlation between the size of the lesion and the depth of invasion, thereby yielding a prognostically useful parameter (Table 4; $P < .01$).

Cellular Pigment Production and Clinical Pigmentation

The presence or absence and the intensity of pigmentation of the primary lesion, as noted by the clinician, were recorded for many patients. Pigmentation of a malignant melanoma is the result not only of melanin in the tumor cells but pigment deposition in the junctional cells at the periphery of the malignant portion of the lesion or pigment deposited in chromatophores. Not surprisingly, the cellular pigment production, which was established on microscopic examination, closely followed clinical pigmentation of the primary cutaneous lesion. Analysis of the available data for 60 patients yielded $P < .01$ (Table 5).

Table 4—Correlation Between Size and Level of Invasion

	Size of nodular or invasive portion			
Level	<5 mm	5–9 mm	>9 mm	Total
II	24	0	0	24
III	17	11	4	32
IV	2	13	11	26
V	1	6	11	18
Total	44	30	26	100

In 7 cases the level could not be determined; in 17, the size could not be determined; in 5, both the level and size could not be determined.

$P < .01$

Table 5—Correlation Between Cellular Pigment Production and Clinical Pigmentation

Cellular pigment production	Clinical pigmentation		Total
	Black/brown	Pink	
None/slight	27	10	37
Moderate/marked	23	0	23
Total	50	10	60

$P < .01$

Other Features Examined

Sex and Prognosis

Of the 80 males and 39 females in our study, the prognosis was poorer for males. The 5-year actuarial survival rate for clinical stage I cases was 83% for women and 66% for men, although the difference between survival rates in the two groups was not statistically significant.

Cell Type and Prognosis

The lesions were classified as being composed mainly of either epithelioid or spindle cells. A third group was also established in which approximately the same number of spindle and epithelioid cells were present. The most common cell type was epithelioid, seen in 65 tumors. The cell type seemed to have no appreciable effect on prognosis.

Cell Type and Mitotic Rate

Although estimation of the mitotic rate of tumor cells is subjective, an attempt was made to grade each lesion with respect to the number of mitoses. Fifty-four lesions were given a low, 40 a moderate and 18 a high mitotic index; no mitoses were seen in the remaining seven lesions. No correlation was observed between mitotic rate and the type of cells composing the melanoma (spindle, epithelioid or mixed).

Lymphocytic Reaction and Prognosis

Due to the importance of immunologic mechanisms, the degree and type of cellular inflammatory reaction associated with the base of the tumor were also studied. In 97 of the 119 cases there was lymphocytic reaction. This response was slight in 51 instances, moderate in 34 and marked in 12. However, the extent of the cellular response seemed to have no effect on prognosis.

Cell Type and Lymphocytic Reaction

No correlation was observed between cell type and the extent of lymphocytic reaction.

Cell Type and Cellular Pigment Production

Similarly, there was no correlation in our data between cell type and cellular pigment production.

Clinical Pigmentation and Prognosis

There were 45 patients in clinical stage I who had a black or brown lesion, and 8 whose lesion was pink or colorless. The survival curves for the two groups were nearly identical.

Treatment

The initial treatment of the primary lesion was classified into three categories: a) inadequate, b) adequate without lymph node dissection and c) adequate with lymph node dissection. Of the 104 clinical stage I patients, 12, 69 and 23 fell into these 3 categories, respectively. Although consideration of treatment modalities was not one of the objects of this study, we checked to make sure that the distribution of the modes of treatment (for all characteristics examined for their prognostic significance) was similar for the groups under comparison. The same analysis, incidentally, was carried out with respect to levels of invasion, since the latter had been shown to have an effect on prognosis. The problem of elective lymph node dissection was also studied in terms of our data, and our results have been reported by Donnellan *et al.*[23]

Discussion

Recently there has been considerable interest in the classification of malignant melanoma as melanoma arising in Hutchinson's melanotic freckle (lentigo maligna melanoma), superficial spreading melanoma (premalignant melanosis, Pagetoid melanoma) or nodular type of melanoma.[1,2,7,24] Our study confirms reports by others that the three types of melanoma represent three different patterns of growth and clinical behavior of the malignant melanoma. While the classification of malignant melanoma into three types is of fundamental importance in the biologic growth potential of the lesion, the histologic features of the invasive (nodular) portion of the tumor are much more significant in determining the further treatment and prognosis of the individual patient.[23] It has been clearly demonstrated, previously, that

the intraepithelial component of the lesion precedes the invasive component.[25]

The larger the lesion, the greater the likelihood of ulceration occurring; this should be noted in making the clinical diagnosis of malignant melanoma. Microscopic examination can determine whether it is due to the complete penetration of the epidermis by the tumor, or whether it is associated with an acute or chronic inflammatory cell reaction due to trauma. This study emphasizes that ulceration of the surface in a malignant melanoma, characterized microscopically by a dissolution of the epidermis, is an ominous clinical sign indicating that the malignant melanoma cells are actively penetrating the underlying dermis. The deleterious effect of ulceration on prognosis can best be explained by the clear correlation between ulceration and the depth of dermal invasion. The deeper the lesion penetrated the dermis, the greater the likelihood for surface ulceration. Aggressive tumors extended both deeply and towards the surface.

It has now been adequately established by several excellent studies [1,2,7,24,26] that estimating the depth of invasion of the lesion into the dermis or subcutaneous adipose tissue is of paramount importance in determining the prognosis. Similarly it has also been shown that the cross-sectional area of the invasive portion of the malignant melanoma is of definite prognostic value.[27] A detailed division of the depth of dermal invasion into 4 or 5 levels should be carried out in both retrospective and prospective studies. There is a clear-cut need for international standardization of the determination of the level of tumor invasion.

In our study, the lack of a statistically significant relationship of the type of melanoma and sex to the prognosis, although previously reported,[1,7] may be due to the smaller number of cases. McLeod,[28] for example, reports 5-year survival rates for male and female patients (all sites) that are almost identical to ours, but his results are based on a total of 1378 cases. A correlation between the type of malignant melanoma and the depth of dermal invasion was clearly demonstrated. Perhaps, to say that the patient's prognosis is related to the level of invasion and also to the type of melanoma is to look at this problem from two different angles. Furthermore, as we did not observe a significant prognostic difference between levels of invasion III and IV, we may be justified in suggesting that these two levels be amalgamated.

The pattern of tumor cells, whether spindle, epithelioid or mixed, showed no prognostic significance. There seemed to be no ad-

vantage in distinguishing between spindle or epithelioid melanoma cells as major components in the primary lesions. The most common cell type was epithelioid, a finding noted also by others.[26,29]

The histologic criteria for diagnosis of the three types of invasive malignant melanoma are now well established and readily reproducible. It should be emphasized that these criteria entirely ignore the association of malignant melanomas with junctional nevi and the Mishima [30] concept of nevocytic and melanocytic origin of pigmented lesions. The term "intraepithelial component" replaces the junctional activity designation.

Admittedly, there are some practical problems involved in this method of reporting the histogenetic designation of malignant melanomas and combining it with microstaging by depth of invasion. But because of its relative ease and clarity the method is expected to gain world-wide recognition and acceptance. Many cases could be unsuitable for either typing or staging due to technically poor histologic preparations, nonrepresentative sectioning, etc. It must, however, be added that in the vast majority of the cases studied and reported by us, a single histologic section sufficed to determine both parameters. In numerous instances the biopsy material preceding the definitive surgical treatment proved to be adequate to render the required histologic typing and staging of the lesion.

This oversimplified method of classifying not readily classifiable, complex malignant melanomas provided a prognostic guide for clinical management, proving its usefulness in this rather limited retrospective study.

References

1. Clark WH Jr, From L, Bernardino EA, Mihm MC: The histogenesis and the biologic behavior of primary human malignant melanoma of the skin. Cancer Res 29:705–726, 1969
2. Clark WH Jr, Mihm MC Jr: Lentigo maligna and lentigo-maligna melanoma. Am J Pathol 55:39–67, 1969
3. Davis J, Pack GT, Higgins GK: Melanotic freckle of Hutchinson. Am J Surg 113:457–463, 1967
4. Fitzpatrick TJ, Brown TC, Reid J: Malignant melanoma of the head and neck: a clinicopathological study. Can J Surg 15:90–100, 1972
5. Jackson R, Williamson GS, Beattie WG: Lentigo maligna and malignant melanoma. Can Med Assoc J 95:846–851, 1966
6. Lane N, Lattes R, Malm J: Clinicopathological correlations in a series of 117 malignant melanomas of the skin of adults. Cancer 11:1025–1043, 1958
7. McGovern VJ: The classification of melanoma and its relationship with prognosis. (Unpublished data)

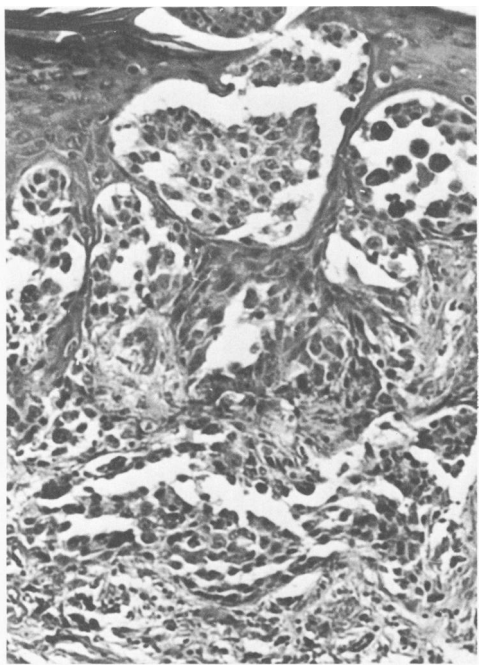
8. Mehnert JH, Heard JL: Staging of malignant melanoma by depth of invasion. Am J Surg 110:168–176, 1965
9. Wayte DM, Helwig EB: Melanotic freckle of Hutchinson. Cancer 21: 893–911, 1968
10. Cutler SJ, Ederer F: Maximum utilization of the life table method in analyzing survival. J Chronic Dis 8:699–712, 1958
11. Gehan EA: A generalized Wilcoxon test for comparing arbitrarily singly-censored samples. Biometrika 52:203–223, 1965
12. Allen AC, Spitz S: Malignant melanoma: a clinicopathological analysis of the criteria for diagnosis and prognosis. Cancer 6:1–45, 1953
13. Ballantyne AJ: Malignant melanoma of the skin of the head and neck: an analysis of 405 cases. Am J Surg 120:425–431, 1970
14. Catlin D: Cutaneous melanoma of the head and neck. Am J Surg 112: 512–521, 1966
15. Catlin D: Melanomas of the skin of the head and neck. Ann Surg 140: 796–804, 1954
16. Conley JJ, Pack GT: Melanoma of the head and neck. Surg Gynecol Obstet 116:15–28, 1963
17. Lund HZ, Kraus JM: Melanotic Tumors of the Skin. Atlas of Tumor Pathology, Section 1, Fascicle 3, Armed Forces Institute of Pathology, Washington, DC, 1962, pp 1–134
18. Petersen NC, Bodenham DC, Lloyd OC: Malignant melanomas of the skin. Br J Plast Surg 15:49–111, 1962
19. Simmons JN: Malignant melanoma of the head and neck. Am J Surg 116: 494–498, 1968
20. Southwick HW, Slaughter DP, Hinkamp JF: Malignant melanomas of the skin of the head and neck. Am J Surg 106:852–855, 1963
21. Queensland Melanoma Project: Moles and malignant melanoma: terminology and classification. Med J Aust 1:123–124, 1967
22. McNeer G, Das Gupta T: Life history of melanoma. Am J Roentgenol 93:686–694, 1965
23. Donnellan MJ, Seemayer T, Huvos AG, Miké V, Strong EW: Clinicopathologic study of cutaneous melanoma of the head and neck. Am J Surg 124:450–455, 1972
24. Little JH: Histology and prognosis in cutaneous malignant melanoma. Proceedings of the International Cancer Conference, Sydney, Australia, 1972, Sydney, Government Printer, 1972, pp 107–119
25. Trapl J, Palecek L, Ebel J, Kucera M: Origin and development of skin melanoblastoma on the basis of 300 cases. Acta Dermato-Venereol 44:377–380, 1964
26. Cochran AJ: Malignant melanoma: a review of 10 years' experience in Glasgow, Scotland. Cancer 23:1190–1199, 1969
27. Breslow A: Thickness, cross-sectional areas and depth of invasion in the prognosis of cutaneous melanoma. Ann Surg 172:902–908, 1970
28. McLeod GR: Factors influencing prognosis in malignant melanoma.[24] pp 367–373

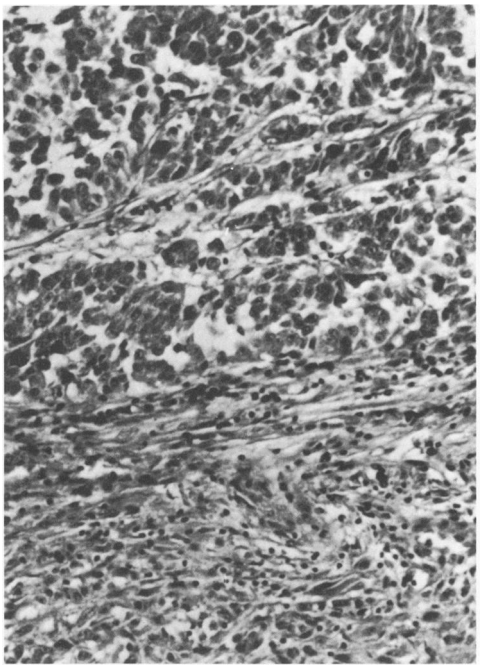
29. Beardmore GL, Quinn RL, Little JH: Malignant melanoma in Queensland: pathology of 105 fatal cutaneous melanomas. Pathology 2:227–286, 1970
30. Mishima Y: Melanocytic and nevocytic malignant melanomas: cellular and subcellular differentiation. Cancer 20:632–649, 1967

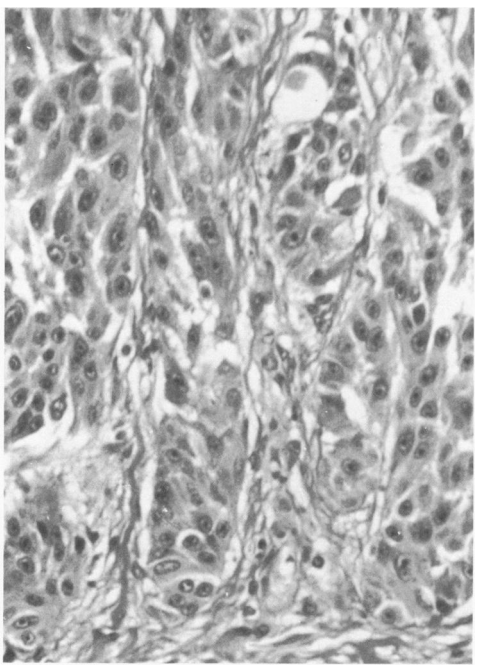
Acknowledgments

The authors are grateful to Pat Middleman for her technical assistance in the preparation of the paper.

[Illustrations follow]







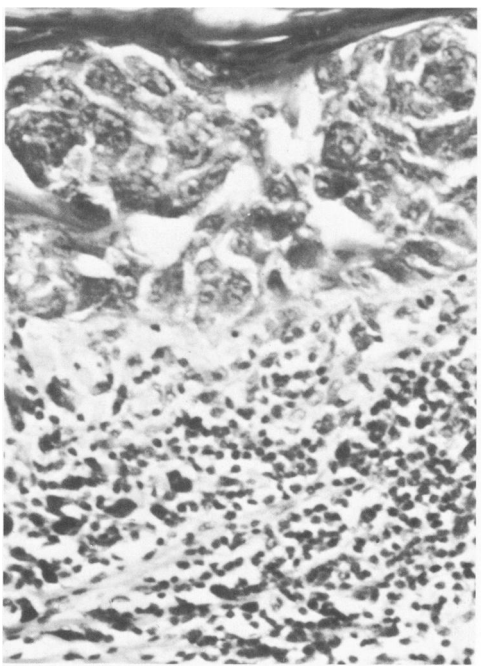
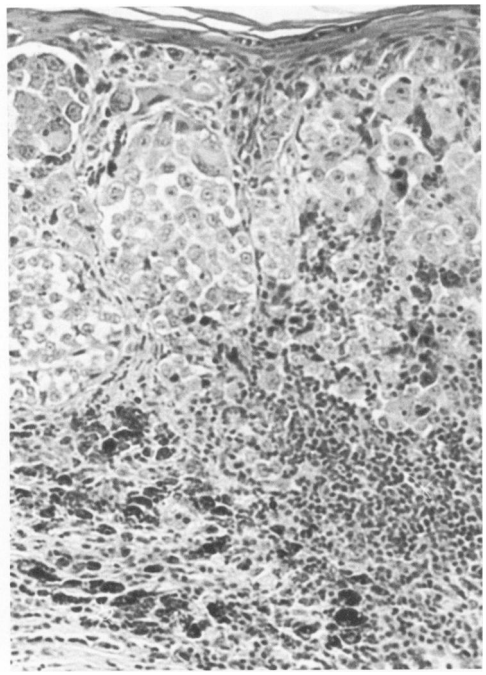
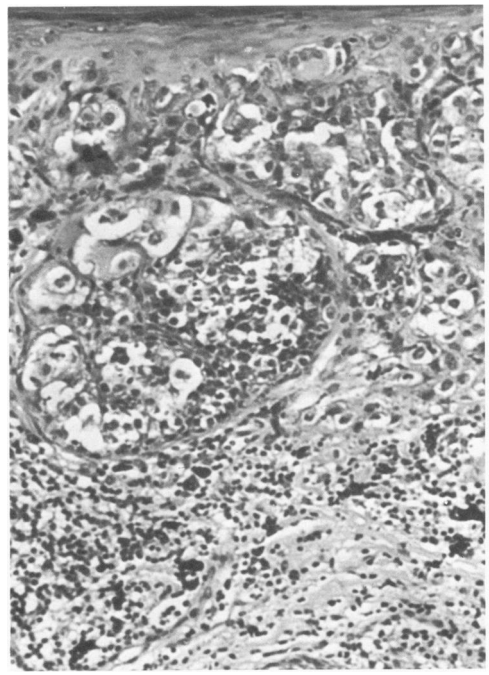


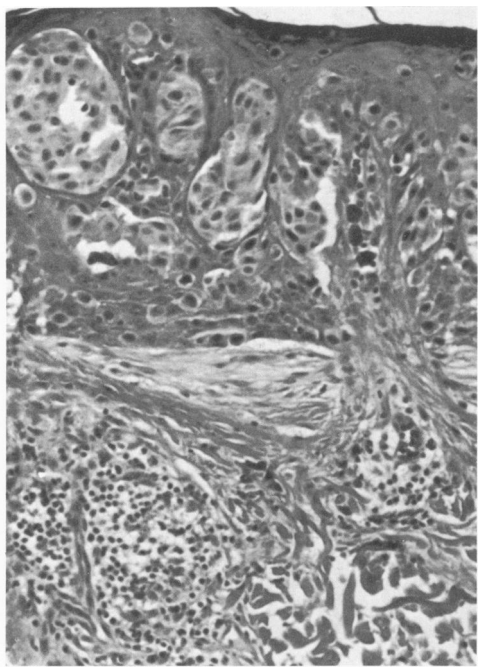
Fig 1—Nodular type of malignant melanoma, with epidermal invasion (H & E, × 50). **Fig 2**—The invasive portion of nodular melanoma with a mixed, spindle and epithelioid tumor cell pattern (H & E, × 80). **Fig 3**—The invasive portion of nodular melanoma with a pleomorphic epithelioid growth pattern (H & E, × 80). **Fig 4**—Malignant melanoma arising in Hutchinson's melanotic freckle. The lesion here is large intraepidermal with questionable dermal invasion (H & E, × 80).



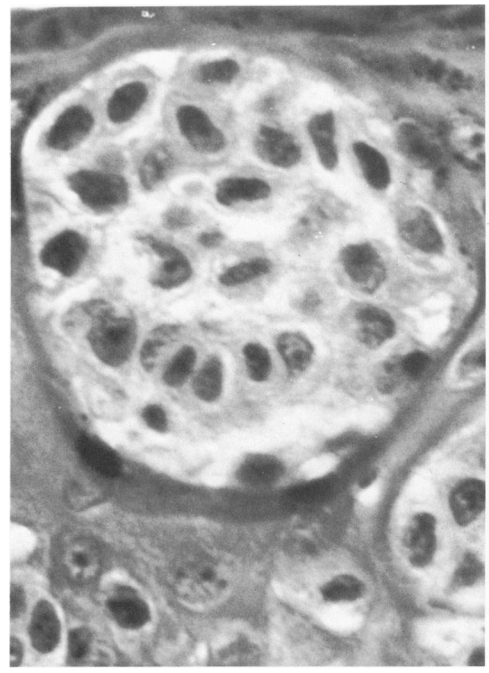
5



6



7



8

Fig 5—Malignant melonoma arising in Hutchinson's melanotic freckle with a predominantly epithelioid growth pattern of the invasive portion (H & E, × 80). **Fig 6**—Superficial spreading malignant melanoma with invasion into lower papillary dermis (Level III) (H & E, × 50). **Fig 7**—Superficial spreading malignant melanoma. The lesion is intraepithelial in this section. Note the Pagetoid tumor cells (H & E, × 80). **Fig 8**—Intraepidermal portion of superficial spreading melanoma. There is a striking resemblance to Paget cells (H & E, × 200).