The Histogenesis and Biologic Behavior of Primary Human Malignant Melanomas of the Skin

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SUMMARY

This paper describes the histogenesis of 3 forms of human malignant melanoma: superficial spreading melanoma, nodular melanoma, and lentigo maligna melanoma. A comparative analysis by computer of the biologic behavior and clinical characteristics of the different neoplasms has been done. An additional 60 tumors have been studied by serial block sectioning. Evidence is presented suggesting that superficial spreading melanoma and lentigo maligna melanoma (Hutchinson’s melanotic freckle), though evolving at different rates, show a long period of superficial growth, followed by the relatively rapid appearance of nodules or deeper invasion within the primary lesion. This change in the nature of the primary lesion may be due to the appearance of one or more strains of cells of aggressive biologic potential. Thus the primary melanoma may exist for a relatively long period of time during which host selective forces act to permit the growth of quite malignant strains of cells. It is these cells that seem to be capable of deeper growth. The subdivision of each of the forms of melanoma into 5 anatomic levels of invasion permits the accurate assignment of prognosis to each case. It is suggested that melanomas are tumors of the epidermal melanocytes and are not necessarily derived from melanocytic nevi. Each melanoma has a distinctive clinical appearance, even in its superficial and curable phases, and this appearance is the same whether or not the process arose in association with a melanocytic nevus.

INTRODUCTION

This paper describes 3 different malignant tumors affecting the human epidermal melanocytic system. These neoplastic processes are described under the terms superficial spreading melanoma, nodular melanoma, and lentigo maligna melanoma (Hutchinson’s melanotic freckle or circumscribed precancerous melanosis of Dubreuilh). Each of these tumors has a recognizable appearance in the patient, distinctive microscopic characteristics, and to a certain extent unique fine structural features. The history of the evolution of each of the primary neoplasms is different, and each has a predictable biologic behavior. Furthermore, within each kind of tumor, behavior may be accurately predicted by the depth of invasion of the neoplastic cells. Finally, various clinical characteristics such as location and age also serve in distinguishing the various melanomas.

We shall also discuss the relationship of the junction nevus to malignant melanoma. It is our opinion that the junction nevus has no formal histogenetic relationship to malignant melanoma. Only in the bathing trunk nevus is there a high incidence of malignant melanoma and the tumors arising in these lesions are of no statistical importance in the overall problem of melanoma. We regard the majority of melanomas as malignant neoplasms of epidermal melanocytes. This pigment-synthesizing system has a specific distribution throughout the normal epidermis (27, 39, 40), and the cells of the system may be found in a variety of cutaneous lesions including the intradermal component of various nevi. Regardless of where melanocytes are located, in normal skin, in freckles, in pigmented nevi, or in other benign lesions, the etiologic factors, as yet largely unknown, that cause melanoma can act upon these melanocytes. The concept of the junction nevus as a premalignant lesion seems to have obscured the fact that most malignant melanomas pass through a long phase of superficial growth during which the process differs in appearance from junctional nevi and is easily recognized on clinical examination.

MATERIALS AND METHODS

This report is based upon the study of 3 series of malignant melanomas observed at the Massachusetts General Hospital. The first series consisted of 96 cases observed prior to Jan. 1, 1958. These cases were selected solely on the basis of the availability of technically satisfactory histologic material of the primary neoplasm and on adequate followup information. The histogenetic concepts underlying much of the present report were formulated through the investigation of the first series of 96 melanomas and have been previously reported in detail (5). These 96 cases have been incorporated with the second series of 113 cases observed between January 1958 and October 1965, and subjected to statistical analysis by computer. The third series of melanomas consists of 60 cases observed from October 1965 through May 1968, which have been studied in detail, clinically and morphologically, but not incorporated into the statistical study because of short follow-
up time. Virtually all of these patients have been seen through the Pigmented Lesion Clinic of the Massachusetts General Hospital and examined personally by at least two of the authors. The examination included a detailed description of the primary lesion, photography of the lesion, examination of the entire skin surface with a count of the nevi present, recording of skin complexion and eye color, and a detailed history of the evolution of the primary lesion. Since we regard the history of the lesion as vital to an understanding of the histogenesis of melanoma, an effort was made to acquire information concerning the total duration of a pigmented spot at the site of the melanoma; i.e., did the process arise from a lesion present from the early years of life or was it of more recent origin? In order to accomplish careful morphologic study of each primary neoplasm, one of us was usually present in the operating room when the specimen was excised and carried it to the laboratory within 3 to 5 minutes after the interruption of the blood supply.

Electron Microscope Studies. The epidermal surface of the specimen was flooded with a 2.5% glutaraldehyde—2.0% paraformaldehyde fixative. The fixative is a slight modification of Karnovsky's method (13). Samples for electron microscopy were then taken. The selection of sites for study by electron microscopy has been a critical step in this investigation. Site selection was not randomly done on the primary lesion. In this study 68.5% (all cases of superficial spreading melanoma and lentigo maligna melanoma) of the tumors had an intraepidermal component well away from the area of invasion. These intraepidermal portions of the neoplasm have been frequently designated in the past as showing "junctional activity" implying origin of the melanoma from a junctional nevus. In most cases, therefore, we have sampled various intraepidermal portions, as well as invasive tumor and normal skin. With experience one can easily recognize with the dissecting microscope an intact basement membrane region, as the basal region appears as a distinct, wavy, pigmented line. Thus one can pre-

OBSERVATIONS

Gross Morphology

Superficial Spreading Melanoma. The outline of these sharply marginated lesions tends to form a portion of an arc of a circle, but a complete circular outline is rarely formed, as a part of the margin is irregular; it is either indented in a reniform fashion, flattened, or shows one or more irregular peripheral-like protrusions (Figs. 1, 2). The surface of the tumor is generally elevated in an irregular fashion some 2—4 mm above the surrounding skin and is therefore easily palpable (Figs. 1, 2, 5). A flat, narrow, tan-to-brown rim at the periphery of the elevated portion may be present (Figs. 3, 5). Some lesions show discrete, circumscribed tumor nodules, which stand out clearly from the remainder of the neoplasm (Figs. 3—5). Such nodules usually have a smooth surface, are pink-grey or dark grey, and may be associated with a history of bleeding. These nodules may develop quite rapidly, usually over a period of 4 weeks to 3 months (Figs. 3, 4), and can be the precipitating factor causing the patient to seek medical attention.

Color is probably the most important aspect of the gross appearance of superficial spreading malignant melanoma. These lesions show a haphazard combination of tan, brown, grey, black, violaceous-pink, and even blue and white. Those lesions showing combinations of the various brown hues, tan through brown-black, may be recognized by the disorganized combinations of these colors (Figs. 1, 2). A transluscent dark grey color is particularly suggestive of melanoma. In addition to flat, violaceous-pink areas, some lesions show discrete, pink amelanotic nodules (Figs. 3, 5). Such nodules may arise in a basically tan-to-brown lesion; and we have seen such patients show metastases of the pink-rose hue (Figs. 5, 6). The colors of blue and white apparently supervene in the course of time upon the variegate admixture of tan, brown, black, and violaceous-pink. These colors are not the direct result of any attribute of neoplastic cells per se, but they indicate the partial disappearance of the tumor and possibly herald the rare, but well-described, regression of the entire primary lesion (23, 38). Here it should be emphasized that the appearance of depigmentation around or within an irregular, disorganized pigmented lesions is virtually pathognomonic of malignant melanoma (Fig. 13) (8). The disorganized depigmentation and pigmentation of a regressing melanoma distinguished this from a halo nevus. Recent publications have discussed depigmentation in the region of nevi and melanomas (15, 37).
Some lesions have a rather scaley surface, giving parts of the tumor a silvery sheen. Occasionally one sees in superficial spreading, lentigo maligna, and nodular melanoma a frankly verrucous surface. Such brown-yellow, irregularly elevated, warty surfaces are confusing and led us at one time, to regard this as a special form of melanoma (5). Now it appears to indicate only an exuberant secondary epidermal hyperplasia that may occur as a part of any kind of melanoma.

**Nodular Melanoma.** This form of melanoma is characterized by a relatively uniform, dark, blue-black color, but has 3 variants in appearance. The first variant is a smooth, uniform nodule, not unlike a blueberry just beneath the epidermal surface (Fig. 7); the second is a quite elevated blue-black plaque with an irregular outline (Fig. 9); while the third is an exophytic, frequently ulcerated lesion (Fig. 8). Nodular melanomas do not have a flat component to the lesion and are quite distinctive on inspection.

**Lentigo Maligna Melanoma.** This tumor frequently covers the largest surface area of any of the melanomas and may be confused with superficial spreading melanoma. It usually shows the same haphazard combination of colors as superficial spreading melanoma, especially tan, brown, reticulated or flecked-black on a brown background (Figs. 10, 11). Blue and white are also seen, and discrete blue-black tumor nodules (Fig. 12) frequently appear late in the course of the disease. In a separate publication we will detail the differences between superficial spreading melanoma and lentigo maligna melanoma, but three points of difference in gross appearance should be emphasized here. First, the outline of lentigo maligna melanoma is everywhere irregular. Superficial spreading melanoma is in part arciform in outline. Second, the surface of lentigo maligna melanoma is mainly flat, while most of the surface of superficial spreading melanoma is elevated. Third, lentigo maligna melanoma shows primarily various shades of brown, while superficial spreading melanoma may show, in addition, violaceous-pink to rose colors.

**Light Microscope Characteristics.** Histologic sections representing the various gross patterns of the primary lesion are necessary for accurate diagnosis and classification of malignant melanoma. About 70% of melanomas (superficial spreading melanoma and lentigo maligna melanoma) have a significant portion of the primary lesion present either intradermal or just below the basement membrane. It is the evaluation of these superficial cells that determines the classification of melanoma, for cells comprising the tumor nodules and invading deeply may appear similar regardless of whether they are from superficial spreading, lentigo maligna, or nodular melanoma.

**Cell Types.** Any of the melanomas described may show 3 different kinds of cells: epitheloid, spindle, and small cells. These cell varieties are recognized most easily where the tumor is in the dermis, but epitheloid and spindle cells may be identified when entirely within the epidermis. The epitheloid cells are large, about 15 to 20 μ in width, with an abundance of dusty, tan cytoplasm (Fig. 14). The nuclei are also large with prominent nucleoli. Spindle cells are strikingly elongated and fibroblast-like (Fig. 15). Melanin may be finely divided or clumped. The small cells, which the Australian workers (36) call nevus-like melanoma cells, are the most difficult to recognize. They are usually no more than 6 to 10 μ in diameter. Nuclei make up the majority of the cell, and they are surrounded by a small amount of cytoplasm, containing little or no pigment (Figs. 16, 17). These small cells may at times be disposed in packets of 3-5 having a somewhat whorled arrangement. Thus far we find no clear association between cell types and the kind of melanoma, except perhaps a tendency for spindle cells to be more common in lentigo maligna melanoma and epitheloid cells to be more common in superficial spreading melanoma.

**Pigmentation.** The definition of amelanotic melanoma is not easy, and, for practical purposes, may be impossible. Perhaps the only accurate way to designate a tumor as amelanotic is at the fine structural level, where one could say that complete lack of melanization of Stage II melanosomes (6, 29) comprises the amelanotic state. Even with this rigid definition the sampling problem in electron microscopy is so great that no pigment was seen at a magnification of X 400 the tumor was classified as amelanotic. A judgment was made concerning pigmentation on 197 of the 209 cases. In only 16 (8.1%) was there no pigment. Most of the primary lesions of the 60 cases of melanoma seen since October 1965 have been examined by us, and the majority have also been examined by the serial block technic. There are no primary tumors in this group that we judge to be completely free of pigment.

**Superficial Spreading Melanoma.** The intraepidermal portion of this neoplasm shows a pagetoid distribution of malignant melanocytes, usually associated with nests of melanocytes (Fig. 18). At all levels of the epidermis, including at times the stratum corneum, one sees relatively large melanoma cells. These are frequently distributed as individual cells; they may be disposed in rather well-circumscribed nests; or the cells may be contiguous with each other, largely replacing the keratinocyte cell population (Fig. 19). Most of the intraepidermal cells are of the epitheloid cell type having an abundance of cytoplasm, usually showing the "dusty" appearance of finely divided melanin. The nuclei are large, at times irregular, and have one or more prominent nucleoli. Mitotic figures, though frequently seen, are not particularly numerous. Careful attention to nuclear morphology may be quite important in histologic diagnosis, for occasional melanocytic nevi, especially from children under 5 years of age, may show a pagetoid distribution of melanocytes; but in these nevi, nuclei are not particularly abnormal.

One of the distinctive features of the intraepidermal cells just described is their relatively uniform appearance in relationship with each other (Figs. 14, 18, 19). Though clearly abnormal, contiguous cells tend to be similar, which is in contrast to lentigo maligna melanoma where there is more variation in cell structure (Figs. 24, 26). Stated another way, the
Intraepidermal cells of superficial spreading melanoma seem to be relatively monomorphic when compared with the pleomorphism of lentigo maligna melanoma. The strictly intraepidermal portions of the neoplasms are not commonly associated with much inflammation of the dermis. In many section plans through superficial spreading melanoma there is no invasion. When invasion is present, cells similar to the intraepidermal melanoma cells are found in the papillary dermis (Fig. 29). These may be contiguous with each other, may lie in cords, or may be scattered as individual cells. Regardless of their distribution they are invariably associated with a dense population of inflammatory cells, including lymphocytes, histiocytes, plasma cells, mast cells, and melanophages. This admixture of inflammatory and neoplastic cells is particularly characteristic of tumors invasive to Level II (Fig. 29). As the tumor begins to fill the papillary dermis and tumor cells begin to accumulate at the interface between papillary and reticular dermis (Level III), the cells show a tendency to form small, discrete nests (Fig. 33).

Grossly, many of the primary lesions show discrete tumor nodules. Microscopically, such nodules are composed almost entirely of tumor cells and these cells are not admixed with many inflammatory cells (Fig. 32). However, the nodules are divided into a number of smaller cell nests by a delicate stroma, which may contain a few inflammatory cells. At times one is impressed by variation in cell morphology from one nest of cells to the next. For example, some nests may show little or no pigment while others are pigmented. The base of the tumor nodules seems, occasionally, to be at the interface between papillary and reticular dermis (Fig. 32); or, from the base, strands of tumor cells may intrude between the collagen bundles of the reticular dermis (Level IV); or there may be an extension well into the subcutis (Level V). The epidermis capping the tumor nodule may be ulcerated or flattened and showing few intraepidermal tumor cells.

**Nodular Melanoma.** The primary tumor is characterized by being uniformly invasive. In fact, the demonstration of dermal invasion throughout the lesion, wherever there is intradermal growth, is nodular melanoma by definition. If this growth extends beyond the width of 3 rete ridges in any section, the tumor is classified as a superficial spreading melanoma. The intraepidermal growth overlying the invasive tumor may be so sparse as to suggest that the lesion is metastatic. The majority of nodular melanomas extend to or into the reticular dermis or into the fat; i.e., they are Level III, IV, or V tumors (Fig. 36). We have classified only one nodular melanoma as Level II.

The tumors which are "blueberry-like" in their gross appearance (Fig. 7) show microscopically numerous small tumor nests admixed with inflammatory cells (Fig. 20). These tumor nests in aggregate form the single gross nodule. The cells at the base of the tumor as a rule intrude between collagen bundles of the reticular dermis (Level IV) or go into the fat (Level V). The large exophytic tumors usually show the base of the dermal tumor at the interface between papillary and reticular dermis (Level III), but commonly there is extension into the subcutis (Fig. 36). The blue-black, nodular melanomas which are irregular in outline (Fig. 9) have a rather unusual histologic appearance. Much of the tumor is located in the papillary dermis with little evidence of intraepidermal growth. One gets the impression that the tumor arose from a rather small intraepidermal focus, invaded the papillary dermis, and then spread laterally for some distance in the papillary dermis with little tendency to deeper extension. Also in these tumors, wherever there is intraepidermal tumor there is neoplasm in the subadjacent dermis.

**Lentigo Maligna Melanoma.** The intraepidermal portions of lentigo maligna melanoma have a variable appearance. In many areas, generally corresponding to a gross appearance of tan or brown, one sees only an increased number of melanocytes in the basal regions (Fig. 21). Even as far as 1.0 cm peripheral to the gross margins of the lesion, one may demonstrate an increased number of melanocytes and even atypical melanocytes (Figs. 22, 23); cells such as these may be seen in the normal exposed aging skin without a recognizable melanocytic neoplasm (27). Such cells are usually disposed individually, being separated from each other by one or more keratinocytes. Within the lesion itself, the melanocytes may vary markedly in form; some appear essentially normal; others have large nuclei or may be multinucleated (Fig. 24). Dendrites are rather easily demonstrated (Fig. 25), and pigmentation of the basal regions is usually well developed. In other intraepidermal areas the melanocytes may be so numerous as to virtually replace the basal keratinocytes, forming an almost continuous melanocytic area separating the keratinocytic epidermis from the dermis (Fig. 24). Collections of quite atypical melanocytes may also form irregular intraepidermal nests (Fig. 26). Pagetoid growth of cells, showing cells at all levels of the epidermis including the stratum corneum, so characteristic of superficial spreading melanoma, is quite uncommon in lentigo maligna melanoma.

When the cells break through the basement membrane, extending into the papillary dermis, they are frequently spindle-shaped, deeply pigmented, and associated with a dense collection of a variety of mononuclear inflammatory cells (Fig. 27). In other areas the invading cells may form discrete tumor nodules and, except for a greater incidence of spindle cells (Fig. 15), are quite similar to tumor nodules of superficial spreading and nodular melanoma. A detailed description of the histology of lentigo maligna melanoma is given in a separate publication.

**Evidence for the Resolution of Primary Malignant Melanoma.** It has been established that primary malignant melanomas may disappear, with or without associated metastases (23, 38). This disappearance is seen as blue translucent areas and white areas in and around the primary lesion. In our experience this phenomenon has occurred only in superficial spreading and lentigo maligna melanomas. Histologically, the blue translucent areas show an essentially normal epidermis, except for diminished pigment and some effacement of the rete Malphigi (23, 26). Below this epidermis there are numerous melanophages, but few inflammatory cells and no demonstrable tumor cells (Fig. 28). The white areas, whether within the tumor margins or around it, show an essentially normal, but pigment-free, epidermis and a dermis of almost normal structure. It would seem that the blue and white areas within the tumor arise following the destruction of invading tumor cells by the host. The pigment from the destroyed cells is phagocytized forming melanophages responsible for the translucent blue areas. As these migrate away, a nonpigmented, but essentially normal, skin remains. The white areas, at times surround-
izing the tumor, are apparently due to inhibition of normal melanogenesis in the area. The phenomenon seems analogous with the series of events occurring in a halo nevus (15).

Certain Fine Structural Features

It is not one of the objectives of this paper to discuss our fine structural studies of human malignant melanoma, but we would like to refer to certain observations to help clarify a single point. This point is the differentiation between the intraepidermal cells of superficial spreading melanoma and cells similarly located in lentigo maligna melanoma; and, further, to distinguish both of these kinds of melanoma cells from the melanocytes of a junction nevus. The intraepidermal cells of superficial spreading malignant melanoma show numerous melanosomes in their cytoplasm. One gets the impression that over 50% of the cytoplasmic cross-sectional area is made up of melanosomal profiles. These numerous melanosomes are quite abnormal. Filaments are formed showing a distinctive periodicity similar to that of the normal, but the filaments do not show cross-linkage. Melanization of these abnormal pigment synthesizing organelles is incomplete, and, consequently, the pigment found in adjacent keratinocytes is abnormal.

In lentigo maligna melanoma the intraepidermal melanocytes show a variable picture. Some cells approach normal, but in many instances nuclei are quite large with a narrowed perikaryon. The nuclear envelope of many cells shows a complex infolding. In spite of these rather striking cellular abnormalities, melanosome formation approaches normal; filaments form and cross-linkage is easily demonstrated; melanization of the organelle is usually complete. When melanosomes are transferred to the keratinocytic system; however, they are not aggregated in the normal way. Instead of a packet of 2—3 melanosomes as is common in light skin, (Y. Hori, personal communication) huge collections of 10—50 melanosomes are seen.

The melanocytes of a junction nevus are essentially normal in every respect, except they have more melanosomes than melanocytes outside the nevus (25). The details of melanocytic fine structure mentioned here have been discussed and illustrated in a separate publication (6).

Levels of Invasion and Prognosis

Several workers have clearly shown that prognosis in malignant melanoma is related to the depth of invasion of the tumor (1, 16, 22, 34, 42). This has also been our experience. The 5 anatomic levels which we use and the reasons for their use are now described.

Level I. All the tumor cells are above the basement membrane. This, by definition, is in situ melanoma. There are no cases included in this study of in situ melanoma. An example of an area which could be classified as Level I is shown in Fig. 18.

Level II. The neoplastic cells have broken through the basement membrane and extended into the papillary dermis but have not gone to the reticular dermis (Fig. 29). An occasional cell or even a strand or small nest of cells may extend to the reticular dermis, and the tumor will still be classified as a Level II lesion. It is only when cells begin to accumulate at the interface between papillary and reticular dermis that the tumor is classified as Level III.

The papillary dermis (papillary layer or body) is not always recognized as such by pathologists, even though it is described clearly in virtually all standard tests dealing with the anatomy of the skin (28). The papillary dermis is that delicate connective tissue just below the basement membrane, and is formed of unit fibrils of collagen, small elastic fibers, and an abundance of ground substance (Figs. 30, 31). The papillary dermis is recognized in sections of normal skin stained with hematoxylin and eosin as a narrow, rather homogeneous pink area, parallel to and just below the epidermis (Fig. 31). The papillary dermis is one of the most characteristic features of the skin of man, for in many mammals distinct papillary and reticular layers are not formed (28). Invading neoplastic cells from the epidermis have their first contact with mesenchymal tissue in the papillary dermis. The demonstration of melanoma cells in the papillary body is the first unequivocal evidence of invasion. It is to be recalled that the papillary dermis extends in a sheath-like fashion around skin appendages. Melanoma cells at times grow along the various skin appendages, especially the external root sheath of pilar units. Extension from these sites into the papillary dermis immediately surrounding the appendages is also considered as only Level II invasion.

Level III. This level is the somewhat ill-defined interface between papillary and reticular dermis; it is the site where collagen begins to be organized into bundles (Figs. 30, 31). This is the only level we use which is different from the levels used by the Australian workers in this field (36). We use this level because we have seen a number of melanomas where the base of the tumor seemed to form almost a straight line and impinge upon the upper part of the reticular dermis without showing any significant invasion of the reticular dermis (Fig. 32, 33). Our statistical studies suggest that it is justified to use Level III as a separate category.

Level IV. Extension to this depth shows neoplastic cells between the bundles of collagen characteristic of the reticular dermis (Fig. 34, 35). Some isolated intrusion of cells between collagen bundles of the upper reticular dermis at the base of Level III tumors is not considered sufficient for classification as a Level IV lesion. There should be distinct invasion well into the reticular dermis.

Level V. Tumors classified as Level V have invaded into the subcutaneous tissue (Fig. 36). There are two ways that levels of invasion have been used by us which reflect prognosis. First, we classified all melanomas, regardless of type, by invasion level and correlated this information with the followup data. Of the 208 cases assigned a definite level, 36 cases were Level II. Of these cases, 3 (8.3%) died of melanoma and had a median survival time of 1.50 years from the date of histologic diagnosis to death. Twenty-six (72.2%) of the Level II melanoma cases are alive and disease free, having a median followup of 6.83 years. Seven (19.4%) of this group with superficially invasive tumors are either dead without evidence of melanoma, dead of unknown causes, or lost to followup. Throughout the remainder of the paper such patients are referred to as the "other" category. Most of this category of patients are those dead of diseases...
other than melanoma. We have calculated the median time between histologic diagnosis and time of placement in the “other” group; this usually indicates the elapsed time between diagnosis and death due to causes other than melanoma. The median time for “other” cases of Level II tumors was 6.42 years.

The data for the patients with Level III tumors were as follows: 71 cases; 25 (35.2%) were dead of melanoma, having a median survival time of 2.08 years; 33 (46.5%) were alive without melanoma, having a median survival time of 6.38 years; 13 (18.3%) were in the “other” category with a median time from histologic diagnosis until being placed in that category of 5.00 years.

The Level IV tumor data were: 76 cases; 35 (46.1%) were dead of melanoma with a median survival time of 2.25 years; 24 (31.6%) were alive without melanoma, having a median follow-up time of 5.21 years; and 17 (22.4%) were in the “other” category, being placed there at a median time of 4.17 years after histologic diagnosis.

The Level V data were: 25 cases; 13 (52.0%) were dead of melanoma with a median survival time of 1.83 years; 3 (12.0%) patients were alive without melanoma with a median survival time of 3.50 years; and 9 (36.0%) patients were in the “other” category, having been placed there at a median time of 1.92 years after histologic diagnosis.

The survival data for all 208 cases by level of invasion is indicated in Chart 1. The failure of the comparative columns to add up to 100% is due to the “other” category referred to above. It is worthwhile pointing out again that the median survival time of patients at Levels II, III, and IV is 6.83, 6.38, and 5.21 years respectively, while that of Level V is 3.50 years. It is, therefore, quite likely that 1 or more of the 3 surviving Level V patients will die of melanoma.

We have in this series of 209 melanomas 114 superficial spreading melanomas, and this is a large enough sample to be statistically significant when studying prognosis by invasion levels. The exact data follow: Of the 114 cases, 22 were Level II; 2 (9.1%) of these died of melanoma, surviving a median time of 1.21 years from histologic diagnosis; 17 (77.3%) were alive without melanoma, having a median follow-up time of 7.24 years; 3 (13.6%) patients were in the “other” category having been placed there at a median time of 7.67 years after histologic diagnosis. There were 47 Level III cases, and of this number, 14 (31.9%) were dead of melanoma, having a median survival time of 2.08 years; 21 (44.7%) were alive and free of melanoma, having a median follow-up time of 6.50 years; while 11 (23.4%) were in the “other” category, having been placed there at a median time of 6.50 years after histologic diagnosis. There were 37 patients with Level IV tumors.

Of these 15 (40.5%) have died of melanoma, having a median survival time of 2.58 years after histologic diagnosis; 14 (37.8%) are alive and free from melanoma, having a median survival time of 3.17 years; and 8 (21.6%) are in the “other” category, having been placed there at a median time of 6.42 years after histologic diagnosis. Eight (7.0%) patients with superficial spreading melanomas were at Level V. Of these 4 (50.0%) are dead of melanoma, having a median survival time of 1.42 years; 1 (12.5%) patient is alive without melanoma 3.50 years after histologic diagnosis; and 3 (37.5%) are in the "other" category, having been placed there at a median time of 2.67 years after histologic diagnosis.

The correlation of levels of invasion and survival data are summarized graphically in Chart 2. In studying this chart one should compare the median survival times of the patients alive without melanoma: Level II, 7.25 years; Level III, 6.50 years; Level IV, 3.17 years; Level V, 3.50 years. It is quite evident that additional Level IV and V patients will die of melanoma, making even more significant the evaluation of prognosis by designating invasion levels.

Relationship of Nevi to Malignant Melanoma

There are written statements (1) and the widespread assumption that malignant melanomas invariably arise from nevi. Implicit in these opinions is the concept that a junction nevus is a premalignant lesion. Our evidence, histologic and clinical, does not indicate that melanomas universally arise in nevi; an opinion shared by several other investigators (11, 17, 18, 41). In fact, origin from a nevus may be the exception rather than the rule. Of the series of 209 cases, 20 (9.6%) showed the unques-
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(P<0.029)

Chart 2. This chart is comparable to Chart 1, and one should refer to the legend of Chart 1 and to the text for details.

DEATHS

SURVIVORS

LEVELS OF INVASION

FREQUENCY OF MELANOMA TYPES

Chart 3. The chart shows the relative frequency and mean age of the various melanomas. SSM, superficial spreading melanoma; NM, nodular melanoma; LMM, lentigo maligna melanoma.

Clinical Characteristics of the Various Melanomas

Frequency and Age Incidence. Superficial spreading malignant melanoma is the commonest form in this series, forming 54.5% of the cases, and the patients had a median age of 56.0 years and a mean age of 52.9 years. The youngest patient was 12 years old and the oldest 87. Nodular melanoma formed 31.6% of the cases, and the median age of these cases was 49.0 years while the mean age was 51.8 years. The youngest patient was 16 years old and the oldest 84. Lentigo maligna melanoma comprised 13.9% of the cases with a median age of 70.0 years and a mean age of 70.0 years. The youngest patient was 45 years old and the oldest 96. These findings are summarized in Charts 3 and 4.

Prognosis and Kind of Melanoma. The comparative mortality rate due to melanoma of the tumor varieties was as follows: Superficial spreading melanoma, 31.5% (36 of 114 cases); nodular melanoma, 56.1% (37 of 66 cases); lentigo maligna melanoma 10.3% (3 of 29 cases). The comparative survival (free of melanoma and without any recurrences) figures were: superficial spreading melanoma, 46.5% (53 of 114 cases), having a median follow-up 6.00 years; nodular melanoma 27.3% (18 of 66 cases), having a median follow-up time of 6.58 years; lentigo maligna melanoma, 55.2% (16 of 29 cases) having a median follow-up time of 4.75 years. The cases neither dead of melano-
noma nor alive without disease had the following disposition: 22 died of causes other than melanoma at a mean time of about 5 years after histologic diagnosis; 9 died of unknown cause at a mean time of about 2 years after histologic diagnosis; 10 are disease free at a mean time of about 7 years after histologic diagnosis but a recurrence was treated during that time; and the status of 3 cases is unknown. The mortality and survival data are given in Chart 5.

**Sex Distribution.** The disease is slightly more common in the female than in the male. Specifically, lentigo maligna melanoma and superficial spreading melanoma have an incidence of about 45% for males and 55% for females, while nodular melanoma is about 53% for males and 47% for females. As has been noted by several workers, the disease is somewhat less malignant in the female when compared with the male (20, 33). Of 106 females in the total series, 35 have died of melanoma, while 40 of 98 male patients have succumbed to the disease (see Chart 6).

**Regional Distribution.** The exact details of the regional distribution of the various kinds of melanoma are given in Chart 7. There are two points concerning distribution that should be emphasized. First, lentigo maligna melanoma is a disease of the exposed surfaces of the body, and, as a corollary of this, it comprises almost one-half of the melanomas of the head and neck. It is this high incidence that is probably responsible for the good prognosis of head and neck melanomas in other reports (3, 31), but these have failed to distinguish lentigo maligna melanoma as a separate entity. It should be pointed out that lentigo maligna melanoma may occasionally occur on nonexposed surfaces of the body. Wayte and Helwig (43) have reported several cases, and we have seen two cases (not in this series), one on the back and the other on the foot. Our case on...
the back, however, was in an elderly male with an almost lifelong history of sun exposure of much of the trunk and extremities.

Second, we should like to call attention to the high incidence of melanoma on the lower legs of female patients (9, 33, 34). Of 32 malignant melanomas on the lower leg, 26 were in females and only 6 in males. Of the 26 melanomas on the lower legs of females, 19 were superficial spreading melanoma, 6 nodular melanoma, and 2 lentigo maligna melanomas.

Treatment and Prognosis. It is not an objective of this study to evaluate forms of therapy. We do not feel, however, that different forms of therapy have played a significant role in prognosis of tumors with different levels of invasion. As a matter of fact the Level II tumors seem to have had somewhat less radical therapy (a higher proportion of local excisions and radical excisions without node dissections) than Level III, IV, or V tumors. Furthermore, if the observations reported in this study are confirmed by others, it seems reasonable to suggest that evaluation of therapy may be meaningless unless correlated with the kind of melanoma and its level of invasion.

DISCUSSION

Biologic Significance of the Histogenesis of Malignant Melanoma. The majority of human malignant melanomas (superficial spreading and lentigo maligna melanoma) are characterized by a relatively long period of centrifugally spreading, superficial growth (intraepidermal or just below the basement membrane), during which the tumor is relatively flat but shows variation in color and outline. In time a more aggressive growth pattern supervenes; this is characterized by a change in the surface of the lesion, irregular elevation and discrete tumor nodules appearing, and concomitant invasion to or into the reticular dermis. These two growth phases, plus the unmistakable evidence of partial or complete disappearance of certain primary tumors, have led us to speculate on the biology of this primary neoplasm.

The superficial growth phase may be a period during which the action of host resistance factors has a selective influence on a hereditarily variable population of cells composing the primary tumor. This hypothetical selection period could ultimately result in the outgrowth of a population of cells of greater malignant potential. Stated another way, it is possible that tumors of Levels III, IV, and V are not only a result of the action of host resistance factors but also have a selectional influence on a hereditarily variable population of cells composing the primary neoplasm. This view then regards nodular melanoma as a quite malignant neoplasm from the outset, but it is probably not a different biologic entity when compared with superficial spreading melanoma.

Pigmented Melanocytic Nevi and Melanoma. We regard human malignant melanoma as comparable to other neoplastic systems, being characterized by a series of cellular events affecting a single cell system resulting ultimately in the evolution of a rapidly growing population of cells capable of surviving in tissues and organs different from the tissue of origin. The epidermal melanocytic cell system is a part of the normal epidermis, the main cellular component of melanocytic nevi, and a part of freckles and of a variety of other cutaneous lesions. Wherever epidermal melanocytes are located, including nevi, malignant melanoma may arise (18). All of the forms of melanoma described in this report have been seen arising in association with nevi, but the identical forms have arisen without being associated with a nevus. One may compare, for example, the quite similar superficial spreading melanomas shown in Figs. 1 and 2. The former arose de novo and the latter in association with a nevus. The lentigo maligna melanoma of Fig. 11 arose in association with a nevus, while that of Fig. 12 showed no evidence of an associated nevus. Regardless, therefore, of the precise location of melanocytes giving rise to the various melanomas, the appearance and behavior of the resultant neoplasms are similar.

Classification and Prognosis of Malignant Melanoma. Many studies of malignant neoplasms tend to report similar survival rates, but this is not necessarily the case with malignant melanoma. Recently reported 5-year survival data of this tumor have shown a wide variation (2, 10, 19–21, 31–33). It has been quite difficult to explain this apparently striking discrepancy in survival rates of malignant melanoma. Some factors relating to the variable survival rates are: (a) the inclusion of all sites of primary origin, such as the eye, with the epidermal tumors, (b) inclusion of “in situ” melanoma, and (c) the high
incidence of advanced tumors managed in large treatment centers. In spite of these factors there still appears to be variation in the biology of individual tumors and variation in prognosis regardless of therapy employed. Recently, however, there have been several attempts at clinical and histologic classification which may clarify the seeming inconsistencies in behavior of malignant melanoma. For example, lentigo maligna melanoma (Hutchinson's melanotic freckle or circumscribed precancerous melanosis of Dubreuilh), though known for years by dermatologists, has now been clearly delineated as an entity in several excellent studies (7, 12, 24, 34, 36, 43).

In addition to the studies of lentigo maligna melanoma, there have been several other approaches to the classification of malignant melanoma. Trapl (41, 42) has emphasized that tumors tending to show "horizontal" growth have a better prognosis than those showing predominantly "vertical" growth. Petersen et al. (34), in discussing their Stage 3 melanomas (those showing tumor formation), originally divided them into 2 groups: those with a "pigmented flare" and those without such a "flare." The Queensland group has remarked upon the poor prognosis of pedunculated or polypoidal lesions when compared with other melanomas (N. C. Davis, personal communication).

Our classification of malignant melanoma into 3 distinctive forms is, therefore, similar to the observations of others. First, we also distinguish lentigo maligna melanoma as a slowly growing, relatively benign neoplasm usually on the exposed surfaces of the elderly. It should be clearly noted, however, that the advanced stages of this tumor may give rise to widespread metastases (43). Secondly, we feel that another form of melanoma, superficial spreading melanoma, also shows a relatively long period (6 months to 5 years) of superficial growth and then develops tumor nodules and deep invasion. The term was selected not to indicate a tumor that always remains superficial, but it was chosen to suggest that the early stages of evolution were characterized by centrifugal rather than deep spread. This tumor, to us, clearly corresponds to the "horizontal" growth of Trapl (41), the "lateral junction activity" of Lane et al. (16), and the "pigmented flare" of Petersen et al. (34). Third, those tumors showing a nodular form and a tendency to deep invasion from the outset were termed nodular melanoma. Again this seems to correspond to Trapl's tumors showing "vertical" growth, the tumor formation (Stage 3) without a "pigmented flare" of Petersen et al., and the polypoidal melanomas of the Queensland group.

In addition to the 3 major forms of melanoma, we also classify all melanomas by invasion levels. Several groups have used a similar approach with meaningful results. Petersen et al. (34) described 3 stages: Stage I, no invasion of the dermis; Stage II, invasion of the superficial dermis; Stage III, tumor formation with and without a "pigmented flare." Their 5-year survival data for these stages were: Stage I, 100%; Stage II, 82.3%; Stage III with a pigmented flare, 51.3%; Stage 3 without a pigmented flare, 32.3%. R. A. Peterson (35) reported 24 cases of melanoma that had invaded only the upper third of the dermis, and there were no deaths, but 10 of the 24 cases had been followed less than 5 years. In a particularly useful study, Menhert and Heard (22) divided invasion depth as follows: Group 0, in situ (excluded from statistical evaluation); Group I, invasion of the papillary dermis superficial to the rete pegs, 77.6% survival; Group II, invasion of the reticular dermis superficial to the base of the deepest sweat glands, 38.6% survival; and Group III, invasion of the subcutis, 8.0% survival.

Our levels are quite similar to those of Menhert and Heard and, except for our Level III, identical with those of McGovern (V. McGovern, personal communication). As has been indicated in our description of the various levels, we have seen many cases where tumor cells accumulate at the interface between papillary and reticular dermis. This accumulation is easily recognized and seems to reflect a change in the capacity for tumor cells to survive in the mesenchyme. In addition, the 5 levels we present have been clearly defined by anatomists and, in this study, correlate well statistically with prognosis. These levels can be easily recognized and their application by other groups will ultimately determine their usefulness.

In summary, we now classify human malignant melanoma on the basis of gross examination and multiple histologic sections as superficial spreading melanoma, nodular melanoma, and lentigo maligna melanoma. Invasiveness in each of these groups is further subdivided into Levels I, II, III, IV, or V. This classification serves as an accurate guide to prognosis and may be a reflection of certain basic biologic phenomena occurring in a primary neoplasm.

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REFERENCES

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Fig. 1. Superficial spreading malignant melanoma (R. B.). The lesion shows the frequent, haphazard combination of the colors tan, brown, and black. The borders are slightly scalloped and the surface irregular, especially in the black portion. The entire lesion was malignant histologically, and there was no associated nevus on serial block histologic examination. The lesion was located on the middle of the chest of a 31-year-old Caucasian male and had been slowly enlarging for 3 years. There was no history of a lesion present prior to that time. The marker in this picture and all color pictures (Figs. 1—12) is proportional to 1.0 cm of actual size in the patient, unless indicated otherwise directly above the marker. The histology of a portion of this lesion is shown in Fig. 29.

Fig. 2. Superficial spreading malignant melanoma (T. M.). The lesion is similar to that of Fig. 1, but shows a suggestion of the common reniform indentation on its right side. Several small, distinctly elevated areas are noted in the black region. These generally correspond with invasion to Level III (see text). The paler, circular zone delineated by points is a zone interpreted as beginning tumor regression. The histology of an area similar to this is shown in Fig. 28. The neoplasm was located on the right upper arm, and a pigmented lesion had been present at the site all of the patient’s life. An associated benign nevus was demonstrated histologically. The histology of the tumor is shown in Figs. 14, 18, and 19.

Fig. 3. Superficial spreading malignant melanoma (I. A.). The majority of the irregular tan-brown lesion is flat, but centrally there is an elevated, relatively smooth, pink-grey nodule. The red, ulcerated area in the left upper quadrant of the lesion is a biopsy site. The lesion was located on the inner aspect of the left calf just below the knee of a 44-year-old female. The lesion had been present 5 years without a history of an antecedent lesion. The nodule had appeared and grown rapidly over a 2-month period. Such nodules are invariably invasive at their base to Level III (see Fig. 32) and commonly to Level IV or V. There was no associated nevus on histologic examination.

Fig. 4. Superficial spreading malignant melanoma (R. L.). The irregular border, pink hues, and a large nodule are characteristic. The biopsy site is at the right edge of the lesion. Lesions with this form are regarded as advanced, and the prognosis is poor. The lesion was present on the left breast of a 46-year-old male. It had been present 5 years, but the nodule was said to have appeared only 6 weeks prior to this photograph. The patient had 2 other primary malignant melanomas at the same time, one on the left arm and the other on the back.

Fig. 5. Superficial spreading malignant melanoma (P. G.). The right portion of the picture shows a rather diffuse pink-tan color, and at the arrows one sees rather discrete, pink nodules. Metastases from this tumor were all pink amelanotic nodules (see Fig. 6). The lesion was present in the left mid-back. A lesion had been present at the site since early childhood. Growth had been noted for 6 months, and bleeding was noted for 3 weeks. The neoplasm was associated histologically with a nevus.

Fig. 6. Metastatic amelanotic melanoma (P. G.). The primary lesion giving rise to this metastasis is shown in Fig. 5. Compare the color of the metastasis with the color of the small tumor nodules shown at the arrows in Fig. 5.
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Fig. 7. Nodular melanoma (W. L.). This tumor is smooth and of a relatively uniform, dark thundercloud grey color. The pink hue is not usually present in this form of melanoma and is here due to the inflammation associated with a ruptured epidermal cyst. The lesion had been present for 4 years on the chest of a 33-year-old male. There was no history of an antecedent lesion, and no associated nevus was demonstrated histologically. The histology of this tumor is shown in Fig. 20.

Fig. 8. Nodular melanoma (S. G.). This dark, blue-black, exophytic lesion is the kind of tumor the Australian workers term polypoidal melanoma. It was invasive to Level V (see Fig. 36). The lesion was present on the right cheek of a 76-year-old female and was of 9 months duration. It was elevated 3.7 cm above the surface.

Fig. 9. Nodular melanoma (L. W.). An occasional nodular melanoma is irregular in outline but is still of a uniform, dark, blue-black color. These irregular tumors show some confinement within the papillary dermis but little tendency to intraepidermal spread, as they are everywhere invasive. The central portion of this tumor had invaded to Level IV, and there was metastasis to one axillary lymph node. The tumor had been present for 1 year prior to the time when this photograph was taken. There was no history of an antecedent lesion. It was located on the outer aspect of the right upper arm of a 59-year-old male. The histology of a portion of the tumor is shown in Figs. 34 and 35.

Fig. 10. Lentigo maligna melanoma (W. T.). This form of melanoma, usually on the exposed surfaces of the elderly, is quite irregular in outline and shows a combination of various shades of brown. Pink is usually not seen, and the tumor is generally quite flat when compared with most superficial spreading melanomas (compare with Figs. 1, 2, 4, 5). This tumor was of 5 years duration without a history of an antecedent lesion on the right cheek of a 67-year-old male. The histology of the peripheral, tan portion of the tumor is shown in Figs. 21 and 24.

Fig. 11. Lentigo maligna melanoma (C. B.). The tumor was mostly flat, but there was invasion in the central black area. The characteristic rich hues of brown are well shown. The tumor was associated with a nevus. There had been noticeable, but slow growth for 10 years on the left cheek of a 62-year-old male. The histology of part of the tumor is shown in Figs. 25 and 26.

Fig. 12. Lentigo maligna melanoma (B. C.). This is a picture of a fully developed lentigo maligna melanoma. The flat tan-brown areas still comprise much of the surface area, but solid black areas and tumor nodules have appeared. The lesion had been present at least 5 years on the right cheek of this 80-year-old female. The histology of different parts of the tumor is shown in Figs. 15 and 27.
Fig. 13. Superficial spreading melanoma (P. M.). This mainly tan-brown neoplasm presents an irregular, almost white area of depigmentation in the lower half of the photograph. This irregular admixture of tan, brown, and white is virtually diagnostic of malignant melanoma. The lesion had been growing and changing color on the back of a 38-year-old female patient for 1 year, but a pigmented spot had been present at the site since the early years of life. There was an associated histologic nevus. The histology of the depigmented area is shown in Fig. 28.

Fig. 14. Epithelioid form of melanoma cells, superficial spreading melanoma. These cells have an abundance of dusty, tan cytoplasm, and contiguous cells are relatively uniform in relationship with each other. The clinical lesion showing this histology is shown in Fig. 2 (66-15,471H, T. M.). × 110.

Fig. 15. Spindle form of melanoma cells, lentigo maligna melanoma. These distinctive cells are fibroblast-like and may contain an abundance of rather coarse, granular pigment. The photomicrograph is of a section of the nodule immediately below the eye of the lesion shown in Fig. 12 (66-8504H, B. C.). × 2500.
Fig. 16. Epithelioid and small forms of melanoma cells, superficial spreading melanoma. Just below the epidermis the cells are of the epithelioid type, while deeper in this quite invasive portion of the neoplasm, they are small and nevus like. Some tumors and their metastases are entirely composed of cells of this type. The cells in the square are shown at higher magnification in Fig. 17 (66-3300D, S. D.). × 110.

Fig. 17. Small form of melanoma cells, invasive portion of superficial spreading melanoma. The cells outlined are the same as those outlined in Fig. 16. Their most distinctive feature is a scanty, almost pigment-free cytoplasm. Some nuclei are pycnotic while others are larger and pale without prominent nucleoli or chromatin clumps. × 450.

Fig. 18. Superficial spreading melanoma. In addition to the nests of tumor cells so characteristic of the intraepidermal portions of this neoplasm, one also sees individual cells scattered, pagetoid fashion, at all levels of the epidermis. The photomicrograph is of a section of the lesion illustrated in Fig. 2 (66-15,471F, T. M.). × 110.

Fig. 19. Superficial spreading melanoma. One frequently sees, as is shown here, large nests of tumor cells virtually replacing the epidermis extending from the stratum corneum above to the dermis below. The gross lesion from which this section was prepared is shown in Fig. 2 (66-15,471H, T. M.). × 110.
Fig. 20. Nodular melanoma. This photomicrograph is of a section of the gross lesion shown in Fig. 7. The nodule is composed of small clusters of cells separated by inflammatory cells (65-3703, W. L.). × 160.

Fig. 21. Lentigo maligna melanoma. This photomicrograph is of a section of the peripheral tan area of the lesion shown in Fig. 10. Much of the basal layer is composed of melanocytes. Nest formation and pagetoid growth are less prominent than in superficial spreading melanoma; compare this figure with Figs. 14 and 18 (67-12,473A, W. T.). × 180.

Fig. 22. "Normal" skin, about 1.0 cm peripheral to lentigo maligna melanoma. This photomicrograph is of a section peripheral to the lesion illustrated in Fig. 11. Not only is there an increased number of melanocytes, but at least 3 atypical ones (arrows) may be seen (66-14,655Q, C. B.). × 180.

Fig. 23. "Normal" skin, peripheral to lentigo maligna melanoma. The photomicrograph is of a section of normal skin on the opposite side of the lesion from that illustrated in Fig. 22. At the broad point there is a binucleate melanocyte, while other melanocytes are essentially normal (66-14,655A, C. B.). × 460.
Fig. 24. Lentigo maligna melanoma with involvement of a pilar external root sheath. This photomicrograph is of a section of a tan, peripheral area of the lesion illustrated in Fig. 10. Large numbers of atypical melanocytes are evident, and the common involvement of the external root sheath is shown (arrows) (67-12,473A, W. T.). × 270.

Fig. 25. Lentigo maligna melanoma, showing an area of prominent melanocytic dendrites. This photomicrograph is of a section of a dark brown area of the lesion illustrated in Fig. 11. At the points one may easily see some of the dendrites (66-14,655V, C. B.). × 270.

Fig. 26. Lentigo maligna melanoma, intraepidermal melanocytic nest formation. This photomicrograph is of a section near the central portion of the lesion illustrated in Fig. 11. Melanocytic nests are shown at the arrows. There is more variation in cell structure than one sees in the nests of superficial spreading melanoma and little-associated pagetoid growth. Compare with Figs. 14 and 18 (66-14,655J, C. B.). × 180.

Fig. 27. Lentigo maligna melanoma, invasive spindle cells just below the epidermis. This photomicrograph is of a section of a flat, blue-black area illustrated in Fig. 12. Elongate spindle cells are extending from the epidermis into the dermis (66-8504H, B. C.). × 160.
Fig. 28. Resolution of primary superficial spreading malignant melanoma. This photomicrograph is of a section of the depigmented area shown in Fig. 13. The epidermis is essentially normal without evidence for neoplastic melanocytes. The dermis shows a variety of inflammatory cells, including a few melanophages (68-4428F, P. M.). X 110.

Fig. 29. Level II invasion, superficial spreading melanoma. This photomicrograph is of a section of the tan area near the center of the lesion illustrated in Fig. 1. Nests of the epithelioid form of melanoma cells extend below the epidermis into the papillary dermis. The lower margin of the papillary dermis is where the inflammatory cells abut against (arrows) the collagen bundles of the reticular dermis. See Figs. 30 and 31 (66-3813C, R. B.). X 110.

Fig. 30. Papillary and reticular dermis of normal skin of the upper back; reticulum stain. This stain clearly delineates papillary from reticular dermis. The pale zone just below the basement membrane region shows delicate reticulin fibers, while the dark area below this shows collagen organized into bundles. The ill-defined interface between papillary and reticular dermis is indicated by arrows. This interface constitutes our Level III invasion. See Figs. 32 and 33 (65-6863, K. M.). X 110.

Fig. 31. Papillary and reticular dermis of normal skin of the right upper arm; hematoxylin and eosin stain. The tissue just below the epidermis is pale and delicate without obvious collagen bundles. Deep to this, collagen is organized into bundles, and the upper part of this zone forms an almost straight line with the papillary dermis (small arrows). Piling up of cells at this interface constitutes Level III invasion. The arrows and their respective roman numerals indicate invasion levels. Level V is into fat (see Fig. 36) (66-15,471J, J. M.). X 110.
Fig. 32. Level III invasion, superficial spreading melanoma with tumor nodules with photograph of gross lesion (insert). This photomicrograph is of a transection of a lesion shown grossly in the insert. The base of the nodule impinges upon the reticular dermis (arrows), forming a Level III invasive tumor (65-6863A, K. M.). x 14.

Fig. 33. Level III invasion, superficial spreading malignant melanoma. The nests of tumor cells indicated by arrows abut against the reticular dermis at Level III (66-3300B, S. D.). x 110.

Fig. 34. Level IV invasion, nodular melanoma. This photomicrograph is of a section through the central portion of the lesion illustrated in Fig. 9. At the base (square) there is clearly extension between collagen bundles of the reticular dermis (see Fig. 35) (68-3764M, L. W.). x 53.

Fig. 35. Level IV invasion, nodular melanoma. This photomicrograph is a higher power of a portion of Fig. 35. Tumor cells are between collagen bundles of the reticular dermis. At the time of surgery a lymph node metastasis was present (68-3764M, L. W.). x 230.
Fig. 36. Level V invasion, nodular melanoma. The photomicrograph is of a section through the center of the lesion illustrated in Fig. 8. There is extension through the reticular dermis into the fat (67-11,587C, S. G.). × 11.
The Histogenesis and Biologic Behavior of Primary Human Malignant Melanomas of the Skin

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