Prospectives for cutaneous malignant melanoma
Considerations of the precursor state and heritability

W H Clark
Department of Pathology, Harvard Medical School, The Beth Israel Hospital, Boston, MA, USA, Pathology Services Inc., Cambridge, MA, USA, The Pigmented Lesion Group, University of Pennsylvania, School of Medicine, Philadelphia, PA, USA

A M Goldstein and M A Tucker
Genetic Epidemiology Branch, National Cancer Institute, USA, Bethesda, MD, USA

Each of the discoveries through the years has begotten a series of Gordian knots. We must patiently inspect our new collection of mysteries and focus on those where our efforts may well change the course of the disease to the benefit of affected patients. The proper management of the precursor state, the beginning of the disease, and the patient exploration of the complexities of heritability would seem to be appropriate beginnings.

Neoplastic systems come into being and are manifest through induction, development, and progression. These phenomena of tumor biology are characteristic of neoplasia and may be classified into six categories. The generic categories applicable to all neoplastic systems are indicated by bold face type in the following list.\textsuperscript{1-3} In melanocytic neoplasia, the specific terminology for some of the categories follows the generic category term.

1. Events at the beginning (inductive events)

2. The precursor state

Melanoma development may not be limited to origin from evident
lesions. The entire organ, the skin, is in an altered state and melanomas may from specific kinds of precursor lesions or may arise from altered melanocytes that are not a part of evident precursor lesions.

3. **Primary cancer without competence for metastasis (intermediate lesions):** Malignant melanoma *in situ* and radial growth phase primary melanoma.

This class of lesions in tumor progression has acquired the property of continuous growth, but has not acquired capacity for metastasis. Melanoma *in situ* shows all tumor cells to be in the epidermal compartment, separated from the dermis by the basement membrane. Radial growth phase melanoma is characterized by tumor cells in the epidermis and papillary dermis similar in appearance to the cells of melanoma *in situ*. Although tumor cells extend into the papillary dermis in the radial growth phase there is no evident capacity for growth there and competence for metastasis is not manifest by this stage of tumor development. We have termed these lesions intermediate for their behavior is intermediate between the distal end of precursor state lesions and primary cancer with competence for metastasis. They differ from late precursor lesions in several respects; the most important of which is continuous growth, albeit quite slow, of intermediate lesions when compared with late precursor state lesions. Intermediate lesions lack the manifest competence for metastasis frequently expressed in primary cancers with competence for metastasis.

4. **Primary cancer with competence for metastasis:** Primary melanoma that has progressed to the vertical growth phase.

Vertical growth phase melanoma refers to a stage in melanoma progression that is characterized by dermal invasion; the ability to grow in the dermis; and some metastatic capacity. Vertical growth phase is not a synonym for invasion. Vertical growth phase melanomas not only extend into the dermis, they grow there. The phrase does imply acquisition of metastatic competence, which may or may not be expressed. Invasion and metastasis are separable properties; clearly attested to by the differences between radial growth phase (invasive capacity, but no metastatic capacity) and the vertical growth phase (invasive capacity, competence for growth in a second tissue compartment, the dermis, and capacity for metastasis).

5. **Metastasis**

6. **Metastasis from metastasis**
Under some of the foregoing categories we will discuss current problems in the study of melanoma and delineate reasonable directions for future study.

EVENTS AT THE BEGINNING

The events at the beginning are the interactions between agents or mechanisms (endogenous or exogenous) and the target organ. The result of such interactions is an altered target organ. The alterations constitute a predisposition to the development of malignant melanoma and may or may not be manifested by demonstrable or recognizable lesions or other tissue changes. Recent epidemiologic studies of melanoma have delineated some of the manifest changes in the skin, the target organ for human cutaneous melanomas. The manifest changes constitute most of the known risk factors for melanoma development. The risk factors, with few variations, have been similar in different studies. The risk factors usually include the following attributes:

- An increased number of melanocytic nevi (nevus in this paper are melanocytic nevi) 2–4 mm in width
- An increased number of clinically atypical nevi and dysplastic nevi
- A family history of melanoma
- Freckling
- Fair complexion
- Excessive exposure to sunlight and severe sunburns
- A cutaneous phenotype that burns rather than tans

A review of melanoma epidemiology and risk factors is not one of the objectives of this article. Studies of such factors, however, clearly delineate major problems related to melanoma induction and progression. Several of these problems are fascinating and these will be discussed.

THE PRECURSOR STATE

One of the most intriguing, and largely unappreciated, aspects of tumor biology is the manifestation of the very beginnings of neoplasia: the initial response to inductive agents and mechanisms is not cancer. Rather, the agents induce the precursor state. As a generality, the development of cancer, itself, is rare when compared with the evident lesions of the precursor state. Thus, the precursor state and
its lesions are most often end stage phenomena, they are not 'pre-
anything'. Premalignant lesion', with its obvious semantic infer-
ence, is the usual term for some lesions of the precursor state and
the term is an egregious misnomer. The precursor state is an organ-
wide alteration which predisposes the organ to the development of
cancer; in the context of this paper a predisposition to the devel-
opment of primary cutaneous malignant melanoma. The precursor
state may not be apparent or it may be manifested by the various
proliferative lesions and atypical cells of the melanocytic system that
are confined to a single tissue compartment and only grow for a
limited time (growth is temporally restricted or constrained). When
growth ceases the precursor lesions become indolent or quiescent.

[A tissue compartment is composed of one or more cellular pheno-
types in organized array separated from an adjacent tissue com-
partment by a basement membrane. When one states that a
proliferative lesion of the precursor state is confined to a single tissue
compartment, the foregoing definition of a tissue compartment is
usually satisfactory. For example, the parenchymal cells of a tubular
adenoma of the colon are all separated from the lamina propria by
a basement membrane. However, on causal inspection, the definition
is not applicable to a compound nevus or a dermal nevus ( nevus
refers to a melanocytic nevus in this paper) Studies have shown,
however, that dermal nevic cells are surrounded by a basement
membrane; in this sense they are still within the epidermal tissue
compartment.]

The atypical cells of the precursor state, when present, may be
within clinically manifest (macroscopic) lesions or they may be scat-
tered throughout an organ in individual cell array (microscopic
lesions). A cutaneous phenotype manifested by freckles, sun sen-
sitivity and solar degeneration of the dermis is also a predisposition
to melanoma development; a precursor state without nevi Pro-
gression to cancer from a given precursor lesion or from a precursor
state without melanocytic nevi is optional, not obligatory.

Organ-wide alteration

Organ-wide, in the present context, refers to alteration of all epi-
dermal and dermal structures, epithelial and mesenchymal. Thus,
the alteration characterized by increased melanoma susceptibility
may not be confined to a demonstrable lesion, such as some form of
a melanocytic nevus. The evidence supporting the concept of organ-
wide is as follows. Even though there is wide variation in the reported
number of melanomas associated with nevi, all studies concerned
with the association of nevi and melanoma have some subset of cases wherein the melanoma develops without an associated nevus. Further, some white children and teenagers (and many black children and teenagers) have no melanocytic nevi on examination by trained observers. It follows that some melanomas develop in skin without a demonstrable precursor lesion at the site of the melanoma or elsewhere on the skin. In addition, we have personally observed and photographically documented patients with many clinically atypical nevi who, in follow-up, developed a melanoma at a site where there was no previously visible precursor lesion. In fact, it has been stated that all of the known risk factors account for only about one half of melanoma cases. We regard this figure as low, but are fully aware that a significant number of melanomas arise in patients that lack most of the known risk factors for the disease. Studies of induced neoplasia in experimental animals and studies of in vitro transformation also indicate that a precursor state (incipient neoplasia) is induced in that portion of an organ exposed to a carcinogen. Foulds defined incipient neoplasia (the precursor state) as a region coextensive with the area of exposure to carcinogenic treatment that has a permanent replicable new reactivity or increased capacity for neoplastic development. In vitro, increased saturation density and growth constraint, X-ray treatment, and chemical carcinogens induce a state of incipient neoplasia in all treated cells not just the cells of transformed foci.

Clinical and histologic definitions of melanocytic precursor state lesions

In the previous section there was evidence presented suggesting that the entire organ, coextensive with exposure to the inductive mechanism, is altered. However, in practice, the existence of the precursor state and its potential for progression to melanoma is based upon recognizable lesions. The most important of these lesions are common nevi, clinically atypical nevi, and dysplastic nevi. Other melanocytic lesions, such as small and large congenital nevi may be precursor lesions and may indicate a precursor state, but will not be considered here. There are problems with terminology applied to the cells composing melanocytic nevi and with definitions of common nevi, clinically atypical nevi, and dysplastic nevi. Our usage of terms and our definitions follow.

The terminology of cells composing nevi

A chronic problem with the terminology of the cells in nevi exists. The intraepidermal melanocytes arrayed as single cells in nevi are
difficult to distinguish from some melanocytes in the epidermis adjacent to the nevus. Consequently, many observers simply call this intraepidermal population of nevic cells, melanocytes. The superficial cells in the dermal component of a nevus synthesize pigment, but do not have the form of melanocytes with dendrites. Further into the dermis, the nevus cells are rounded, lack pigment, or tyrosinase, and differentiate into elongate cells that are Schwannian in character. Some authors call the cells in the dermis (and epidermis) nevomelanocytes, even though most of the cells have few properties that may be rightfully regarded as those of dendritic intraepidermal melanocytes. One could designate all of the cells as nevic cells of melanocytic origin and designate their location. Such a descriptive designation is semantically cumbersome. We refer to the intraepidermal cells of nevi as melanocytes, either in single cell array or in nests. The cells in the dermis are termed dermal nevic cells. We are not satisfied with any terminology, including our own, and lean toward descriptive designations for accuracy in transmission of concepts.

Definitions of lesions and disorders manifested by the lesions

Common nevi—clinical definitions. The following definition of a nevus is acceptably vague and comprehensive, but it lacks precision. A melanocytic nevus is a sharply circumscribed area where there is a great increase in the number of melanocytes and nevic cells in the surface epithelium, or in the dermis, or in both epidermis and dermis, when compared with the surrounding, unaffected skin. Melanocytic nevi may be found in the skin, in the mucosae, and rarely in other tissues and organs.

- Lentigo and junctional nevus
  The lesions are sharply delineated, oval or circular in outline, dark tan or brown. Angulation is rare. They are flat or barely palpable. By definition, for this report, the lesions are ≤4 mm in width. Lesions ≥4 mm in width, along with other characteristics given later, are, again by definition, clinically atypical nevi. Different observers use a different size for the designation of a lesion as clinically atypical; ≥5 mm in width seems to be the most common size in use as one of the criteria for clinical atypia.

- Compound nevus and dermal nevus
  The lesions are also sharply delineated, usually circular in outline, brown, dark brown, or flesh colored. They are elevated and may
be polypoidal, but, if the latter, have a stalk virtually the same width as the lesion.

**Common nevi – histologic definitions.** The descriptions in standard texts of cutaneous pathology usually give 4 histologic kinds of nevi. This statement does not include congenital melanocytic nevi, blue nevi and several other diverse and uncommon nevi. Some texts separate the simple lentigo from the other histologic appearances of nevi. We regard the lentigoes and junctional, compound, and dermal nevi as one distinctive category of melanocytic proliferation presenting in different stages of evolution. Circumscribed melanocytic proliferations begin with an increase in the number of basilar melanocytes associated with elongation of rete (in other words, as a lentigo) and may progress to junctional, compound and dermal nevi. The incidence of such progression is totally unknown and available evidence suggests that this process of evolution may become arrested at any stage. Thus, one may have a lentigo or compound nevus, for example, that is stable for years. All nevi in the group we are discussing here are common, appear in the first three decades of life, and may or may not be related to the cutaneous effects of light.

- **Lentigo**
  The hallmarks of a lentigo are an increased number of melanocytes along regularly elongated rete and increased basilar pigmentation.

- **Junctional nevus**
  A junctional nevus shows an increased number of intraepidermal melanocytes disposed in nests. The cells in the nests are lymphocyte-like, being small, with a scanty amount of cytoplasm. Dendrites are not observed. The individual cells of the nests are no larger than the usual, inactive basilar melanocytes of the epidermis. The nests tend to be equally spaced and at the tips of rete. As will be discussed, lesions fulfilling the foregoing histologic criteria are rare and the entity still exists more through custom than evidence or even conventional wisdom.

- **Compound nevus**
  The intraepidermal melanocytic component is similar to that just described for an idealized junctional nevus. The cells of the dermal component, just below the epidermis, are round, delimited by a basement membrane and variably pigmented. Deeper in the dermis, the pigment is absent and, still deeper, some of the cells are elongated and show various neuroidal forms. Such a deep component is usually interpreted as showing Schwannian differentiation.
Dermal nevus
There is no epidermal melanocytic component, but the epidermis may be hyperpigmented. The lesion is similar to the dermal component of a compound nevus, but neurotization tends to be more prominent.

The weakest link in the evolutionary chain of nevi is the junctional nevus. Meticulous search of a large histologic collection of cutaneous pigmented lesions by one of us has shown but the rarest example of a junctional nevus with the histologic criteria given above (WHC). Further, a careful histologic systematist (Aldo Gonzales-Serva, personal communication, 1994) has told us that he has difficulty with the histologic diagnosis of a junctional nevus and rarely makes such a diagnosis, without qualification.

Clinically atypical nevus. The clinically atypical nevus is \( \geq 4 \) mm (others use \( \geq 5 \) mm) in diameter and has a macular component and two or more of the following characteristics: an irregular border, an indistinct or hazy margin, two or more tan-brown colors, and erythema

Dysplastic nevus. A dysplastic nevus shows an array of intraepidermal melanocytes that is different from that seen in a lentigo or compound nevus. The different array may be seen as irregular nests of melanocytes along the margins of rete or over dermal papillae or as a bridge of melanocytes extending from one rete to the next. In addition, readily discernible atypical melanocytes must be seen in those areas showing the different disposition of intraepidermal melanocytes. The subjacent dermis is altered. The fibroblasts, both bipolar and dendritic, are increased in number. The collagen may appear as an intensely eosinophilic band parallel with the epidermal basal layer, or as parallel layers of collagen and bipolar fibroblasts (lamellar fibroplasia). Scattered patches of lymphocytes and macrophages are also seen in the dermis.

Controversies concerning the term dysplastic nevus are discussed with the related controversies concerning the dysplastic nevus syndrome.

Familial melanoma. When a family has two or more first degree relatives with melanoma it is affected by familial melanoma. The existence of familial melanoma does not imply heredity, but does identify kindreds that may be studied for hereditary mechanisms.

The dysplastic nevus syndrome
Dysplastic nevus syndrome was used to designate a familial melanoma family member who had clinically atypical nevi and dys-
plastic nevi. A member of a familial melanoma family who has clinically atypical nevi or dysplastic nevi or both is stated to be affected by the dysplastic nevus syndrome. The term, dysplastic nevus, has been lifted from its histologic context (it is a histologic term) when used to designate the syndrome. Controversies concerning the term dysplastic nevus syndrome, clinically atypical nevi and familial melanoma have been so vigorous that they form a small industry characterized by divisiveness, a profusion of papers, a plethora of terms for the same entity, seminars and large conferences. It would seem unwise to us to continue to use dysplastic nevus syndrome for the following reasons. First, the term implies a common pathway for cutaneous malignant melanoma and dysplastic nevi. This may or may not be true. Both cutaneous malignant melanoma and dysplastic nevi in an individual and in a family are remarkably complex in presentation, histology, and heritable mechanisms. Given such complexity, it is likely that the developmental and even the causal paths of cutaneous malignant melanoma and dysplastic nevi may be intersecting, independent, or overlapping. Secondly, some formal definitions of syndrome state that multiple tissue-organ systems must be involved. Thirdly, familial melanoma may occur without dysplastic nevi, and in this context there can be no relationship between the two lesions. For these reasons, we do not use the term dysplastic nevus syndrome.

In contrast, the histologic term, dysplastic nevus is satisfactory and should be retained for it designates a pivotal lesion of biologic significance, when dysplasia is used as it is in other neoplastic systems. In other neoplastic systems dysplasia designates a class of lesions having considerable propensity for progression to overt cancer. However, even this common usage is associated with controversy that may be quite acrimonious. The controversies are readily understood for dysplasia occurs in the lesions of a grey area in neoplastic development: a vast collection of diverse proliferative lesions that span the broad developmental time zone between induction and cancer. The distal end of the grey area, has lesions that show readily recognizable cytologic atypia, harvests dysplastic lesions. The pathology of the lesions of the distal precursor state is not easy in most neoplastic systems but of great importance, for it informs tumor biology and arguably identifies, with some precision, the lesions and sites most likely to progress to overt cancer. In this regard, Antonioli has stated that many conditions such as atrophy and intestinal metaplasia are associated with gastric carcinoma, '...but only epithelial dysplasia has a
positive predictive value for malignancy. Prominent melanocytic atypia in dysplastic nevi may prove to be as important in melanocytic neoplastic biology and progression as it is in gastric tumor progression and tumor progression in other neoplastic systems. Augustsson et al. found that a single lesion with histologic dysplasia was second only in relative risk for melanoma to ≥3 clinically dysplastic nevi (clinically atypical nevi). In spite of contrary recommendations, the terms dysplastic nevus and dysplasia should be used, for only such use affords some uniformity in terminology and biologic significance from one neoplastic system to another neoplastic system.

Light in relationship to nevi and melanoma

Many epidemiologic studies of melanoma, addressing inductive factors, have been reported, but, thus far, light is the only exogenous inductive agent consistently identified as of significance. The role of light in the induction of melanoma is, to say the least, complex. The following categories include only some of the divergent roles light may play as an exogenous factor in the interactive complexities of melanoma causation.

The induction of common nevi by light

Evidence for induction of common nevi by light. As far as we are able to determine, the foregoing clinical and histologic definitions constitute the lesions ≤4 mm (or ≤5 mm) in width counted and evaluated histologically in most epidemiologic studies of melanoma. There is an abundance of evidence that light plays a significant role in the induction of such nevi (the common nevi). Clinically atypical nevi and dysplastic nevi will be discussed in a subsequent section. Trained observers studying the skin surface routinely and easily note the presence of nevi in areas exposed to the sun and the virtual absence of nevi in areas usually covered by clothing and rarely exposed to light. Methods used in nevic counts vary widely and comparisons of the counts of nevi in various studies are, consequently, of little value. Until methods and ability of observers are standardized, reliable and consistent counts of nevi will be unusual. Augustsson and her associates, however, have done careful studies on a random sample of Swedish people 30–50 years of age and compared the sample with melanoma cases also 30–50 years of age. Their studies afford quantitation of nevic numbers in relationship to exposure to sunlight. Therefore, we will present the results of their
We emphasize that the results of other studies are similar but not so readily quantifiable. The Swedish workers (Augustsson, Sterner, Rosdahl, Suurkla) compared a population sample and melanoma cases. The random sample from the census file in Göteborg resulted in 379 subjects (183 men and 196 women) that could be analyzed: 121 melanoma cases (of 197 original cases from the Regional Cancer Register), who were also between 30 and 50 years of age could be analyzed. The main reasons for exclusion of cases from analysis were death and inability to histologically review or confirm the original diagnosis of melanoma. One specific objective of their studies was to investigate the possible role of UV-irradiation in the development of melanocytic nevi. Another objective of their studies was to evaluate both common nevi and dysplastic nevi as risk markers for melanoma. All subjects were evaluated by a single trained dermatologist and a random sample of 20 subjects was assessed by another dermatologist to assure uniformity in diagnosis and counting. The pathology of all cases was reviewed. The evaluation and counting of nevi was done in two parts:

- All subjects had the macular and raised nevi ≥2 mm in width, of the entire body surface, counted. If there was difficulty in distinguishing between nevi, lentigines, and freckles, the questionable lesion was not counted.

- A different method was used to carefully distinguish between protected and exposed areas. A protected area 14 × 28 cm over the buttocks was compared with an exposed area of the same size on the back, 14 cm above the buttock area. The differences between the exposed and protected areas were expressed as the \( \text{Ex-Pr} \) difference.

The major clinical criterion used to define dysplastic nevi was a diameter ≥5 mm. (These workers use dysplastic nevus as a clinical as well as a histologic term. They give precise definitions for both the clinical and histologic usage.) In addition to size, at least two of the following criteria were required before a lesion was classified as dysplastic on clinical grounds: an ill-defined or an irregular border, speckled pigmentation, erythema or a pebbled surface. The histologic criteria required for classification of a lesion as a dysplastic nevus included:

(a) irregular melanocytic hyperplasia in the basal epidermal layer;
(b) minimal nesting of the increased number of basilar melanocytes;
(c) lentiginous elongation of the rete;
(d) stromal changes including fibrosis and a lymphocytic infiltrate;
(e) a thin dermal nevic component that was not as wide as the epidermal component;
(f) cytologic atypia that was not more prominent than that seen in lentigo maligna.

The criteria are similar to those of Elder and Sagebiel et al. and are not as fully described here as in the original papers. Augustsson and her coworkers have shown a quantitative relationship between light exposure and the number of common nevi. The number of nevi on exposed areas of the body surface was significantly higher than in areas rarely exposed to light. Cutaneous surfaces categorized as having intermittent light exposure (back above the waist, for example) had larger numbers of nevi than chronically exposed areas (face and backs of the hands). Subjects reporting > 3 sunburns had higher total nevus counts than patients with < 3 sunburns. Somewhat surprisingly, chronically exposed areas had about the same number of nevi as areas rarely exposed to light (bathing trunk area and inner aspects of the upper extremity). The 14 × 28 cm defined area on the back, the exposed area, had more nevi than the protected area of the same size on the buttocks. The total number of nevi and the difference in number of nevi between the two areas was greater in melanoma cases than in controls. Also, the number of nevi in both areas was higher in patients with dysplastic nevi when compared with individuals without dysplastic nevi. Dysplastic nevi did not have the same regional distribution as common nevi, none being recorded on the face and they were uncommon on the extremities. While it is hard to disagree with the compelling evidence relating sun exposure to nevi, there has been a study that denies such a relationship. In that work, however, comparative nevic counts on exposed and protected areas were not done; only nevi on the chest, back and legs were counted and the results were related to anamnestic information concerning sun exposure and exposure to artificial sources of UV-light.

The development of melanocytic nevi without the direct effect of light

There is no question, however that nevi develop without any relationship to the direct effects of light. Melanocytic nevi occur in sites with little or no exposure to the direct effects of light. They are relatively common subungually and on the plantar surfaces of blacks and whites, and they are observed in the oral cavity, the vagina, the
perineum and in the capsule of lymph nodes. The origin of nevi without a discernible relationship to UV-light exposure suggests several areas for future study. Such sites are referred to herein as unusual sites.

- What are the inductive mechanisms for nevi in these sites?
- Are nevi in the unusual sites formal histogenetic precursors of melanoma?
- Do they indicate a precursor state for the unusual site?
- One of the more intriguing thoughts concerning nevi in unusual sites is generated by reflecting on nevi in the capsule of lymph nodes. These nevi are composed of small round, pigment-free nevic cells of the kind seen in the mid-portion of dermal nevi. Standard histogenetic thinking concerning the development of the dermal nevus tells us that its component cells arise from the melanocytes of the epidermis, which then migrate into the dermis and form the various structures that constitute a dermal nevus. Such a mechanism could hardly apply to the nevi in the lymph node capsule. What are its origins? Could true dermal nevi in the skin have histogenetic pathways that are different from our maxims?

Experimentally, melanocytic nevi can be induced by chemical carcinogens. Lesions so induced are remarkably similar to common junctional and compound nevi of human skin, and this again attests to the repeated observation that the early manifest lesions of neoplastic systems are similar regardless of the nature of the inductive mechanism. Accordingly, nevi in unusual sites could be related to inductive agents and mechanisms other than light. A search for these disparate agents could be fruitful. It would seem especially important to inquire into the nature of pigmented lesions on the plantar surfaces, and to determine whether or not such lesions are a part of a distinctive precursor state of a melanocytic neoplastic system on the sole of the foot. Mishima and Nakanishi have reported a plantar precursor lesion under the term plantar premalignant melanosis, but a systematic epidemiologic and histologic study of the problem of a precursor state or precursor lesions of plantar melanomas has not been done, to our knowledge. Plantar malignant melanoma seems to be a different form of the disease than that which occurs over the other cutaneous surfaces and for this reason alone the disease on the sole of the foot warrants careful scrutiny. The paper of Lewis' on melanoma in Uganda specifically addressed the problem of precursor lesions of plantar melanoma. He did not use terms commonly applied to nevi, but adopted a grading system for pigmentation of the sole of the foot.
- Grade I  No pigment seen.
- Grade II  Areas of light brown to dark brown pigment of various sizes, often with irregular outlines.
- Grade III  Discrete, small black areas of pigment with clear-cut margins.

The pigmentation varied with age and from tribe to tribe. The feet of children were more or less pigment free. Grade II pigmentation appeared about the time of puberty and became more prominent and common during adolescence. Grade III pigmentation was not commonly observed until the affected individuals were about 20 years of age. Lewis regarded Grade II pigmentation as 'simple melanosis' not related to Grade III pigmentation nor to melanoma. On the other hand he correlated Grade III pigmentation with 'clear cell' hyperplasia and junctional activity. Further, he correlated the site of Grade III pigmentation with sites of plantar melanoma and concluded that Grade III pigmentation was a precursor lesion to plantar melanoma. The observations of Gordon and Henry corroborated Lewis' work. Nevi and melanomas on the sole of the foot have frequently been attributed to trauma to the sole of the foot in the African, but there is little evidence to support this. For one thing plantar melanomas are about as common in whites as in blacks. Even though the vast majority of melanomas in blacks are on the sole of the foot, the incidence of the plantar disease in the two races is probably about the same, at least in North America. If there are differences in incidence of plantar melanoma in different countries and tribes in Africa and if any such differences distinguish the disease from that seen in North American blacks, there would be urgent reasons for appropriate case control studies to tease out suggestions as to causation. In fact, one would hope that future studies of melanoma would focus on disease in unusual sites as being informative of mechanisms important in nevus/melanoma induction other than light and complex heritable factors.

What is a melanocytic nevus?

It is remarkably difficult to answer this question with any confidence that answer is anything but a parroting of conventional wisdom gleaned from any standard text on cutaneous pathology. One problem is the frequently glib assignment by pathologists of pigmented lesions to the categories of lentigo, junctional nevus, compound nevus, and dermal nevus. There are few critical studies of biology, histogenesis, and histology of common nevi. For example, com-
parative histologic studies of nevi, matched by site, age and sex, in different cutaneous phenotypes could be quite informative. What are the differences between nevi located in the scapular area of 16 year old female individuals, one group being black and the other red-haired frecklers? More directly, are there different kinds of common nevi, dependent upon race, inductive mechanisms, or other factors, as yet unknown?

*Is a melanocytic nevus a manifestation of 'spottiness'?* Exposure to sunlight – depending on such factors as dosage, skin color and the like – will evoke melanocytic and keratinocytic mitogenesis as well as pigment synthesis. The tanning response to light occurs more or less uniformly in an area coextensive with the area of light exposure. In addition, exposure of a large area of the skin surface to light will evoke a mild tanning response in a protected area. By inference, systemic factors may be evoked by cutaneous light exposure, including some that are mitogenic. If light is important in nevogenesis and in the responses to light are more or less uniform in the area exposed to light, why is a nevus a *sharply circumscribed* area having a great increase in melanocytic density? Obviously, a similar question may be asked about the initial manifest lesions of any neoplastic system and answers to the question would cover many topics related to cellular injury and necrosis, and to the nature and quantity of carcinogenic stimuli. Here, we would like to focus speculations on focality to the phenomenon of cutaneous spottiness. The late Ian Whimster wrote with remarkable imagination on this topic. Briefly, Whimster showed that many cutaneous diseases, (such as neurofibromas, xanthomas, and the Köbner phenomena) show a 'spotty' quality. When the inductive mechanism is continuous over a given area, say a scratch mark in a patient with psoriasis, the resultant lesions are initially focal (spotty) and not coextensive with the scratch mark. Later the lesions induced by the trauma may or may not become confluent. Whimster posited that spottiness was the result of a response of mosaics forming the skin. He further suggested that there were differential responses between different mosaics, possibly dependent upon neural control. The term mosaicism is most commonly used in a genetic sense today. 'Mosaicism in an individual or in one or more tissues is a condition in which there are two or more cell lines, derived from a single zygote but differing genetically because of post zygotic mutation or nondisjunction.' Whimster viewed the entire human skin as organ having '... a planned and organized composition built up of initially separate pieces with differing qualities, purposefully chosen and individually placed tog-
ether so that together they form a picture or pattern, designed to fulfill an intention.' He showed that reptilian skin was clearly so formed and a spot of a given color was fixed at a site. If the spot was excised the healing skin initially showed no spot, but in time the spot returned exactly as it was before surgery. Spots could either be fixed (the red and green scales of the lizard *Phelsuma laticauda*) or they could come and go (the chameleon, *Chamelo dilepsis*), but the coming and going was always in the same spot. He suggested that human skin was a mosaic and that there could be a differential response of its mosaic tiles (if you will) based upon internal factors controlling the mosaic, factors possibly related to the autonomic nervous system. There are studies of genetic mosaicism in relationship to cutaneous and other diseases and these genetic factors may play a role from time to time in unusual patterns of melanocytic nevi, but Whimster was referring to a mosaicism present in the skin of all individuals having a role in disease manifestation. (See Happle for a discussion of genetic mosaicism and cutaneous disease.) Jean Bolognia and her associates have given us an excellent discussion of Blaschko's lines and these intriguing structures may have some relationship to the mosaicism discussed by Whimster. In fact, Crelin suggested to Bolognia that the lines could represent the distribution of autonomic motor innervation.

**Light and the induction of clinically atypical nevi and dysplastic nevi**

Clinically atypical nevi have a body site distribution that differs from common nevi. They are uncommon on the arms when compared with common nevi, while clinically atypical nevi are more frequent on the buttocks than common nevi. We have also noted clinically atypical nevi and dysplastic nevi (histologic dysplasia) commonly on the covered area of the female breast and in the scalp. It is of considerable interest that melanoma is rare on the covered area of the breast of females in the United States and the buttocks of both sexes. The various discrepancies between the site distribution between common nevi, clinically atypical nevi, and melanoma pose several questions.

**What is the relationship between common nevi and dysplastic nevi?**

Dysplasia may develop in a common nevus that has been present for some years. There is no question that classical dysplasia occurs in association with a classical histologic pattern of a common nevus. It is difficult to prove, however, that the common nevus preceded the dysplasia. If one assumes the common nevus → dysplastic nevus path
to occur in temporal sequence, with a period of quiescence between the two lesions, it follows that the dysplasia is the result of causative mechanisms in addition to those responsible for the common nevus. Consider two different cutaneous phenotypes in support of the foregoing statement. One phenotype is represented by an individual who tans with ease and forms nevi. Many such individuals expose themselves extensively to sunlight and may well have over 100 common nevi, but some individuals with this phenotype, perhaps the majority, do not develop dysplasia. Thus, one important nevogenic agent, light, may not induce a dysplastic nevus even when the dosage is quite high. In contrast, the second phenotype, frequently burns and tans poorly and forms nevi and such nevi may well develop dysplasia. One infers, if not concludes, that the dysplasia developed in this second cutaneous phenotype because of an inherent difference in the skin; a different biological skin from the first phenotype. The difference could well act conjointly with light to induce dysplasia. A further point illuminating differences between ordinary nevi and dysplastic nevi is the natural history of the two lesions. Common nevi do not, as a rule, form after 30 years of age. Dysplastic nevi continue to form in more than 20% of patients > 50 years of age. The foregoing discussion considered light as a force driving nevi to dysplasia. However, ‘spontaneous’ progression from a common nevus to a dysplastic nevus is a significant possibility, at least on theoretical grounds. Compound nevi have spherical nests of melanocytes at the tips of epidermal rete and nevic cells in the dermis. If one conflates such a histologic picture with the life history of some nevi, one may state that the intraepidermal nests of a compound nevus have a great increase in melanocytic density when compared with the adjacent uninvolved epidermis and such a lesion may have ceased growing. A repetitive theme in neoplastic development is growth, cessation of growth, growth, cessation of growth, growth, cessation of growth . . . . Foulds’ has shown that tumor progression occurs in neoplastic systems during periods of growth cessation. Foulds’ Rule III. Progression is independent of growth. Progression occurs in latent tumor cells and in tumors whose growth is arrested. Progression without manifest growth may account for long delayed recurrences and metastases. Progression that is independent of growth may also account for the development of cancer in a precursor lesion that had been stable for years. Foulds also states, in discussing the significance of time in neoplastic development, that neoplastic capacity may increase autonomously with time without repeated carcinogenic stimuli. Strauss has presented evidence that mutation may be time dependent rather than replication dependent.
In an elegant series of in vitro experiments using a subline of NIH3T3 cells, Rubin has shown that increased saturation density and growth constraint will induce transformation with tumorigenic foci similar to the effects of ionizing irradiation or chemical carcinogens.\textsuperscript{37,86,87} One may suggest that events similar to those observed by Foulds in studying experimental rodent mammary carcinogenesis and events observed by Rubin in his in vitro experiments with fibroblasts, occur, from time to time, during nevic growth and cessation of growth. In such instances, one sees a nest of intraepidermal melanocytes. These nests of a compound nevus show small melanocytes crowded into a compact sphere. When compared with the distribution of melanocytes in the adjacent skin, the lesion manifests increased saturation density and may well have ceased growth (growth constraint). With regrowth, the intraepidermal pattern of melanocytes is entirely different and some of the cells are atypical: dysplasia has followed increased saturation density and one or more periods of growth constraint. If such a mechanism is one of the pathways to the development of dysplasia, it would exemplify progression from a compound nevus to a dysplastic nevus without the necessity of further action of additional exogenous agents. The diverse paths of progression to a dysplastic nevus just discussed, further emphasize the complex and heterogeneous nature of nevi, dysplastic nevi, and melanoma. It is likely that all of the paths are operative in the development and progression of the melanocytic neoplastic system.

\textit{Dysplasia may arise concomitantly with the development of a common nevus.} This histogenetic proposal suggests that a common nevus develops and concomitantly shows dysplasia somewhere within the lesion. Direct observations suggest that this may be a common mechanism of histogenesis of dysplasia. The difficulty with such evidence is that most patients subjected to extensive sequential photography are patients from families with heritable melanoma. Nevertheless, we have photographically documented the development of a nevus that was both common and dysplastic. The site of the lesion was the posterior shoulder of an 8 year old girl. The site was photographed showing no manifest lesion. Sequential photographs showed a continually evolving lesion: initially macular; then elevated centrally with a macular periphery; and, finally, irregularity of the border. When excised the central elevated portion of the lesion was a compound nevus and the periphery of the lesion dysplastic. One cannot prove that the common nevus and the dysplastic nevus arose simultaneously, but, in this instance, the two certainly formed a continuum. Such histogenesis implies that the combination of com-
mon nevus and dysplastic nevus may develop simultaneously and, in all likelihood, the inductive mechanisms for both forms of nevi were present at the same time. Such mechanisms could be both endogenous and exogenous. In the instance just referred to, the individual was a member of a melanoma family most of whom had a cutaneous phenotype characterized by: numerous clinically atypical nevi and dysplastic nevi, freckles, difficulty in tanning, and ease of sunburn. Common nevi and dysplastic nevi may develop separately from each other, both spatially and temporally. When this occurs, and it would seem to be the most frequent presentation of common and clinically atypical nevi, one may observe a separate population of common nevi, dysplastic nevi, and lesions that are a combination of the two.

**What is the relationship between light and dysplastic nevi?** In this paper we have reviewed evidence that intermittent light exposure is nevogenic (for common nevi). Is light also an inductive factor for dysplastic nevi? It would seem that both ‘Yes’ and ‘No’ are correct answers to the question.

**Yes.** Weinstock and his associates, as a result of a case control study, stated that sun sensitivity was associated with dysplastic nevi (clinically atypical nevi and dysplastic nevi – 54% showed histologic dysplasia) risk, (clinically atypical nevi and dysplastic nevi – 54% showed histologic dysplasia). Clinical observations showing dysplastic nevi in sites of intermittent sun-exposure provide impressive evidence of a relationship between light and dysplastic nevi.

**No.** We have previously discussed, in this paper, dysplastic nevi occurring on the buttocks, on the scalp and on the covered area of the breasts (of US women). Dysplastic nevi also occur on the vulva. One may conclude that dysplastic nevi do appear where direct light exposure is minimal or absent.

**Is the continuing action of light required as an engine driving common nevi to dysplastic nevi, and, in turn, driving dysplastic nevi to melanoma?** The precursor state of many neoplastic systems seems to be driven forward by the continuing action of its initial inductive mechanisms. The best example of this is the effect of tobacco smoke. Cessation of smoking greatly decreases the subsequent incidence of bronchogenic carcinoma. In this regard, the reader should study the experimental work of Iverson. He has shown that very small doses of DMBA stated to have no promoting potency act synergistically as a strong promoter of DMBA-initiated mouse skin. Thus, the
continuing action of the inductive agent drove the system down the pathroad of tumor progression.

A critical study has not been done wherein patients with clinically atypical nevi and proven dysplastic nevi are protected from light; and patients, so protected, are subsequently shown to have a decreased incidence of melanoma and changing dysplastic nevi. Tucker and her associates have suggested that additional sun exposure is important in the progression from clinically atypical nevi and dysplastic nevi to melanoma. Family members followed prospectively after the family had been shown to be affected by melanoma had a lower incidence of melanoma after 5 years than during the first 5 years of follow-up when compared with the incidence of melanoma in family members prior to knowledge of the family being affected. In addition, those followed prospectively had fewer changing moles and fewer biopsies in the later time periods. Upon questioning, it was discovered that the prospective follow-up group had significantly changed their sun exposure habits early in the follow-up; their insolation was definitely decreased. 

Light and a cutaneous phenotype incapable of forming nevi

The sun-reactive skin types in common usage are:

I. Always burn, never tan
II. Usually burn, tans with difficulty
III. Sometimes burns, tans about average
IV. Rarely burns, tans with ease to deep brown.

There are individuals of types I and II who do not form any nevi. We do not know of any extensive discussion of this phenotype. It is known, however, that such individuals not only develop melanoma, but are at high risk for its development when they have a history of many damaging sunburns. Thus, we have opposed phenotypes: the mucosae and dark brown to black skin form nevi without the direct effects of light and some sun-reactive skin types with significant light exposure cannot form nevi. One may suggest that the latter group has epidermal melanocytes that produce a high level of pheomelanin (aminohydroxyphenylalanine – AHP), as do dysplastic melanocytic nevi. However, work by Salopek et al. indicates that the normal skin of patients with dysplastic nevi had a lower content of pheomelanin than did dysplastic nevi. There are, however, individual cases whose pheomelanin content in their normal skin was as high as the median of the dysplastic nevus cases in the Salopek study. In addition, one cannot tell from their data whether or not they
studied individuals with a cutaneous phenotype that cannot form nevi. Therefore, there is still a possibility that the 'no-mole' phenotype has a distinctive melanocyte, characterized by pheomelanin synthesis.

FATAL MALIGNANT MELANOMA: PRIMARY MELANOMA AND DISSEMINATED METASTATIC DISEASE

Most studies of prognostic factors indicating a high risk of dissemination and death use attributes of the primary melanoma and attributes of the host bearing that melanoma. These factors are now well known and include such features as mitotic count, thickness, sex of the patient, site of the melanoma and other useful attributes. There are not, however, detailed studies of patients and their primaries when the outcome was death due to disease. If such cases be studied in comparison with nonfatal cases (say matched by thickness, mitotic count, host lymphocytic response, site and sex) will a distinctive group of fatal melanomas emerge? Heenan (unpublished observations and personal communication, 1994) has suggested that there may be a core of 'fatal melanoma' in the cases in Western Australia. In that province both the public and the profession are knowledgeable concerning the early stages of the disease, but the mortality rate has flattened in recent years. It has not declined in spite of identification and treatment of the early, 'thin' melanomas.

PROSPECTIVES FOR THE STUDY OF THE MELANOCYTIC PRECURSOR STATE, PRIMARY MELANOMAS, AND METASTATIC MELANOMA

- What are the inductive mechanisms when light apparently has no direct effect?
  (a) Do nevi have a different histogenesis and histology in light skin when compared with dark skin?
  (b) What is the histogenesis of nevi of the mucosae and other uncommon sites, such as the capsules of lymph nodes, when the epithelium has few or no melanocytes or there is no epithelium?
- What alteration of the skin marks the precursor state in interlesional skin?
- What alteration of the skin marks the precursor state when the cutaneous phenotype cannot form common or dysplastic nevi?
• What is the nature of the precursor state when progression to melanoma has been documented?
  (a) Will this nature, if it can be defined, be unique and partially explain the remarkable rarity of progression from the precursor state to overt melanoma?

• What is an atypical cell in a precursor lesion?
  (a) Does such an atypical cell differ from the cells of an overt melanoma?
  (b) Are atypical cells required for melanoma to develop?

• What are the defining characteristics of acral lentiginous and mucosal melanoma?
  (a) What is the precursor state for these distinctive forms of melanoma?

• What is the nature of primary melanomas that lead to disseminated disease?
  (a) Is this a subset of melanomas awaiting delineation?

• Should we all revisit Whimster and the lizard's tail?

HERITABILITY. WHAT IS INHERITED IN FAMILIAL SYSTEMS?

Consider the following aspects of malignant melanoma.

• The interaction of light with white skin of an individual for the first 30 years of life may result in the following different manifestations in the epidermal melanocytic system. The list is partial and does not include tanning or changes in the dermal connective tissue.

  No clinically manifest lesions.
  Freckles, no moles.
  Freckles and moles.
  Common nevi.
  Common nevi and clinically atypical nevi.
  Common nevi, clinically atypical nevi, and dysplastic nevi.

*Malignant melanoma.

  Lentigo maligna type
  Superficial spreading type
  Nodular type.

• Malignant melanoma and nevi occur in sites without a direct effect of light: oral mucous membrane, vaginal mucous membrane, the capsule of lymph nodes, leptomeninges, urinary bladder, gall blad-
der, hepatic and common bile ducts, esophagus, anus, and other sites.

- Nevi and melanomas occur on the plantar surfaces of blacks, as do nevi. Nevi and melanomas may or may not be related in these sites. The incidence of plantar nevi in Uganda varies from tribe to tribe.

- The incidence of melanoma is exquisitely rare when compared with the number of nevi.

If one merges the preceding lists with the fact that no 2 melanomas are alike (as no 2 multicellular organisms are alike) and the fact that only some 8-12% of melanomas are familial, what, from the infinite (the term is used literally) maze of phenomena, is inherited? Even if one adds reasonable constraints to both the speculations and the questions, and addresses only familial melanoma (two or more first degree relatives affected), the problem of heritability in melanocytic neoplasia (and any form of cancer) is still incomprehensibly complex. A common history of melanocytic neoplastic evolution may be seen in children whose families are affected by familial melanoma. The initial manifestation is the appearance of nevi, which arise, enlarge and may merge imperceptibly into clinically atypical nevi and dysplastic nevi (when examined microscopically). Such individuals may not progress to melanoma. Did these children only inherit a predisposition to the development of nevi, clinically atypical nevi, and dysplastic nevi? If so what kind of gene product could be responsible for such a predisposition? Other children, siblings indeed, may have a similar history of nevic emergence and evolution and develop melanoma? Did such children have a different genetic heritability or did environmental factors drive their nevi into melanoma? Then, there are familial melanoma families without clinically atypical nevi or dysplastic nevi. Did they inherit a predisposition to melanoma only? The complexities do not end and cannot be explained by the product of a single susceptibility gene. If such genes are shown to actually exist they are can be but markers of a disorder. Their products are not autonomous forces driving the system. From the foregoing description of the different presentations of familial melanoma, one would assume that the disease is heterogeneous. In fact, a variety of genetic studies confirm this.

**Familial melanoma**

Two of the authors (AMG, MAT) have recently reviewed the genetic epidemiology of familial melanoma. Different methods are used to
demonstrate genetic factors, including the study of tumor tissue for changes in chromosomes, oncogenes, tumor suppressor genes, DNA repair genes, genes controlling the cell cycle (molecular check point genes), and linkages studies. Herlyn has recently reviewed abnormalities in chromosomes, oncogenes, and tumor suppressor genes. Here, we shall discuss linkage studies. In 1989, Bale and her associates demonstrated linkage of a combined cmn/dn (cutaneous malignant melanoma/dysplastic nevus) trait to chromosome 1p markers d1s47 and pnd. One important criticism of Bale’s work was that the objective phenotype of cutaneous malignant melanoma, alone, was not linked to 1p. Although controversy about the matter still exists, linkage of cutaneous malignant melanoma without dysplastic nevi, as a phenotype, has been linked to 1p. Subsequent studies by Cannon-Albright et al and Nancarrow, et al showed linkage of a familial melanoma locus (mlm) to chromosome region 9p13–9p22 near interferon-α (INFα) and d9si26. Quite recent studies by Cannon-Albright and her associates have placed the mlm locus to a 2-cM region between D9S736 and D9S171. A study of the estimated power to detect linkage in different data sets indicated that the discrepant findings in the data sets were likely to be due to genetic heterogeneity rather than spurious results. The p16 CDKN2 gene, a strong candidate for a melanoma tumor suppressor gene, has been localized to 9p21 in the region implicated in melanoma in linkage, cytogenetic and heterozygosity studies. The candidate gene binds to cyclin dependent kinase 4 and, thus, inhibits the activity of certain cell cycle enzymes. In this capacity it may affect the balance between functional p16 and cyclin D and alter growth control. However, the demonstration of involvement of the p16 gene (CDKN2) has been shown in only a fraction of cases. If the p16 gene should actually be shown to be a melanoma tumor suppressor gene in the fraction of cases, its action(s) would fail to explain but the smallest portion of the manifest and manifold phenomena of the disease. Many studies of oncogenes and tumor suppressor genes have only addressed growth in neoplastic systems. However, neoplastic systems are characterized by growth and cessation of growth in repetitive cycles covering years of neoplastic development and progression. Further, the appearance of strikingly atypical cells, some indistinguishable from many cells in fully evolved cancers, apparently occurs in the precursor state during periods of growth cessation. The emergence of such atypical cells precedes fully evolved cancer by years (in human systems).

Presently, it must be concluded that linkage studies show significant evidence of heterogeneity, with some showing linkage to 1p,
others to 9p and others without demonstrable linkage. Explanations
for genetic heterogeneity include the strong possibility that the dis-
ease is actually heterogeneous. We would be surprised if a disorder
as complex as melanocytic neoplasia (or any neoplastic system, for
that matter) would or could have a monogenic explanation Mono-
genic explanations (or searches for a cause or an etiology) for neo-
plastic disease seem to reflect the human mind entrapped in a
theoretical and historical prison of reductionism, and also entrapped
in the contemporary fashion for molecular explanations, rather than
a human mind curiously probing the natural history of a disease as
it actually occurs 3,104

ACKNOWLEDGEMENT

This work was supported by grants from the National Cancer Insti-
tute, USA: CA-58845 and CA-25298.

REFERENCES

1 Clark WH Tumour progression and the nature of cancer Bnt J Cancer 1991,
64 631-644
2 Clark WH, Jr The role of tumor progression in prevention of cancer and
reduction of cancer mortality In Greenwald P, Kramer BS, Weed DL, eds
3 Clark WH, Jr The nature of cancer Morphogenesis and progressive (self-
disorganization in neoplastic development and progression Acta Oncol 1994 (In
press)
4 Guerry D, Synnestvedt M, Elder DE, Schultz D Lessons from tumor pro-
gression – the invasive radial growth phase of melanoma is common, incapable
of metastasis, and indolent J Invest Dermatol 1993, 100 S342-S345
5 Clark WH, Jr, Elder DE, Guerry DI et al Model predicting survival in stage I
melanoma based on tumor progression J Natl Cancer Inst 1989, 81 1893-1904
6 MacKie RM, Freudenberger T, Atchison TC Personal risk-factor chart for
cutaneous melanoma Lancet 1989, 2 487-490
The Danish case-control study of cutaneous malignant melanoma I Importance
of host factors Int J Cancer 1988, 42 200–206
8 Østerlind A Epidemiology of malignant melanoma in Europe Acta Oncol 1992,
31 903-908
9 Lee JAH The melanoma epidemic thus far Mayo Clinic Proc 1990, 65 1368–
1371
240
11 Holly EA, Kelly JW, Shpall SN, Chuu S-H Number of melanocytic nevi as a
468
12 Clark WH, Reimer RR, Greene M, Ainsworth AM, Mastrangelo MJ Origin of
familial malignant melanomas from heritable melanocytic lesions The B-K mole
syndrome Arch Dermatol 1978, 114 732–738
13 Elder DE, Clark WH,, Elenitsas R, Guerry DI, Halbern AC The early and
intermediate precursor lesions of tumor progression in the melanocytic system
Common acquired nevi and atypical (dysplastic) nevi In Cochran A, ed Sem-
inars in Diagnostic Pathology 1993 18-35
14 Grob JJ, Gouvernet J, Aymar D et al Count of benign melanocytic nevi as a
major indicator of risk for nonfamilial nodular and superficial spreading mel-
anoma Cancer 1990, 66 387–395
15 Rigel DS, Rivers JK, Kopf AK et al Dysplastic nevi Markers for increased risk
for melanoma Cancer 1989, 63 386–389
16 Halpern AC, Guerry D, Elder DE et al Dysplastic nevi as risk markers of
sporadic (nonfamilial) melanoma – a case-control study Arch Dermatol 1991,
127 995–999
17 Halpern AC, Guerry D, Elder DE, Trock B, Synnestvedt M A cohort study of
S349
18 Bale SJ, Goldstein AM, Tucker MA Description of the National Cancer Institute
Melanoma Families Cytogenet Cell Genet 1992, 59 159–160
19 Bergman W, Gruss NA, Frants RR The Dutch FAMMM Family Material –
Clinical and Genetic Data Cytogenet Cell Genet 1992, 59 161–164
20 Dracopoulos NC, Bale SJ, Fountain JW Genetic analysis of familial melanoma
In Brandt ML, White R, eds Hereditary Tumors New York Raven Press, 19??,
39–45
21 Goldstein AM, Fraser MC, Clark WH, Tucker MA Age at diagnosis and
transmission of invasive melanoma in 23 families with cutaneous malignant
22 Salmon JA, Rivers JK, Donald JA, Shaw HM, McCarthy WH, Kefferd RF
Clinical Aspects of Hereditary Melanoma in Australian Cytogenet Cell Genet
1992, 59 170–172
23 Weinstock MA, Colditz GA, Willett WC et al Melanoma and the sun – The effect
of swimsuits and a healthy tan on the risk of nonfamilial malignant melanoma in
women Am J Epidemiol 19??; 134 462–470
24 Westerdahl J, Olsson H, Ingvar C, Brandt L, Jonsson PE, Moller T Southern
travelling habits with special reference to tumour site in Swedish melanoma
patients Anticancer Res 1992, 12 1539–1542
25 White E, Kirkpatrick CS, Lee JAH Case-control of malignant melanoma in
Washington State I Constitutional factors and sun exposure Am J Epidemiol
19??, 139 857–868
26 Koh HK, Kligler BE, Lew RA Sunlight and cutaneous melanoma Evidence for
and against causation Photochem Photobiol 1990, 51 765–779
27 Gallagher RP, McLean DI, Yang P et al Suntan, sunburn, pigmentation factors
and the frequency of acquired melanocytic nevi in children Similarities to mel-
anoma The Vancouver mole study Arch Dermatol 1990, 126 770–776
29 Yaar M, Woodley DT, Gilchrist BA Human nevocellular nevus cells are sur-
rounded by basement membrane components Immunohistologic studies of
human nevus cells and melanocytes in vivo and in vitro Lab Invest 1988, 58
157–162
30 Stolz W, Schmoeckel C, Landthaler M, Braun-Falco O Association of early
malignant melanoma with nevocytic nevi Cancer 1989, 63 550–555
31 Sagebiel RW Melanocytic nevi in histologic association with primary cutaneous
melanoma of superficial spreading and nodular types – effect of tumor thickness
J Invest Dermatol 1993, 100 S322–S325
32 Weinstock MA, Colditz GA, Willett WC et al Moles and site-specific risk of
nonfamilial cutaneous malignant melanoma in women J Natl Cancer Inst 1989,
81 948–952
33 Gallagher RP, Rivers JK, Yang CP, Meclean DI, Coldman AJ, Silver HKB
Melanocytic nevus density in Asian, Indo-Pakistani, and white children – The


58 Augustsson A, Sterner U, Rosdahl I, Suurkula M Regional distribution of melanocytic nevi in relation to sun exposure, and site-specific counts predicting total number of naevi Acta Derm Venereol (Stockh) 1992, 72 123–127

59 Green A, Swerdlow AJ Epidemiology of melanocytic nevi Epidemiologic Rev 1989, 11 204–221

60 English DR, Armstrong BK Melanocytic nevi in children 1 Anatomic sites and demographic and host factors Am J Epidemiol 1994, 139 390–401


62 Elder D The dysplastic nevus Pathol 1985, 17 291–297


67 Johnson WT, Helwig EG Benign nevus cells in the capsule of lymph nodes Cancer 1969, 23 747–753


69 Pawlowski A, Lea PJ Nevi and melanoma induced by chemical carcinogens in laboratory animals: similarities and differences with human lesions J Cutaneous Pathol 1983, 10 81–110

70 Pawlowski A, Haberman HF, Menon A Junctional and compound pigmented nevi induced by 9, 10-dimethyl-1,2-benzanthracene in skin of albino guinea pigs Cancer Res 1976, 36 2813–2821


73 Dwyer PK, Mackie RM, Watt DC, Aitchison TC Plantar malignant melanoma in a white Caucasian population Br J Dermatol 1993, 128 115–120


75 Stevens NG, Liff JM, Weiss NS Plantar melanoma: Is the incidence of melanoma of the sole of the foot really higher in blacks than whites? Int J Cancer 1990, 45 691–693

76 Sterner U, Rosdahl I, Augustsson A, KEGedal B UVB irradiation induces melanocyte increase in both exposed and shielded human skin J Invest Dermatol 1989, 92 561–564

77 Whimster IW The mosaic nature of pigmentary change in diseased skin Ann Ital Dermatol Clin Sperimentiali 1960; 16 357–384

78 Whimster IW An experimental approach to the problem of spotness Br J Dermatol 1965, 77 397–420

79 Happle R Mosaicism in human skin – understanding the patterns and mechanisms Arch Dermatol 1993 Nov, 129:1460–1470
83 Rubin H Experimental control of neoplastic progression in cell populations Foulds’ rules revisited Proc Natl Acad Sci USA 1994, 91:6619–6623
85 Strauss BS The origin of point mutations in human tumor cells Cancer Res 1992, 52:249–253
86 Rubin H Experimental control of neoplastic progression in cell populations Foulds’ rules revisited Proc Natl Acad Sci USA 1994, 91:6619–6623
89 Iversen OH A course of very small doses of DMBA, each of them with allegedly no promoting potency, acts with clear synergistic effect as a strong promoter of DMBA-initiated mouse skin carcinogenesis APMIS 1994, 102, Supplementum No 41:1–38
91 Jimbow K, Lee SK, King MG, Hara H, Chen H, Dakour J, Marusyk H Melanin pigments and melanosomal proteins as differentiation markers unique to normal and neoplastic melanocytes J Invest Dermatol 1993, 100:S259–S268
92 Salopek TG, Yamada K, Ito S, Jimbow K Dysplastic melanocytic nevi contain high levels of pheomelanin Quantitative comparison of pheomelanin/eumelanin levels between normal skin, common nevi, and dysplastic nevi Pigment Cell Res 1991, 4:172–179 (See Fig. 1)
93 Elsasser WM Reflections on a theory of organisms Quebec, Canada Editions Orbis, 1987
94 Clark WH Jr What is inherited in neoplastic systems? Animal models of cutaneous malignant melanoma Lab Invest 1994, 71:1–4
96 Herlyn M Molecular and cellular biology of melanoma Austin, Texas R G Landis Co., 1993
97 Goldstein AM, Dracopoli NC, Ho EC et al Further evidence for a locus for cutaneous malignant melanoma-dysplastic nevus (CMM/DN) on chromosome 1p and evidence for genetic heterogeneity Am J Hum Genet 1993, 52:537–550
100 Cannon-Albright LA, Goldgar DE, Neuhausen S et al Localization of the 9p melanoma susceptibility locus (MLM) to a 2-cM region between D9S736 and D9S171 Genomics 1994, 23:266–268


104 Strohman R Epigenesis The missing beat in technology Bio/Technology 1994, 12 156-164