THE Melanocytic Proliferations

A Comprehensive Textbook of Pigmented Lesions

SECOND EDITION

A. Neil Crowson, Cynthia M. Magro
and Martin C. Mihm Jr

WILEY Blackwell

with website

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A Comprehensive Textbook of Pigmented Lesions

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WILEY Blackwell

Published by John Wiley & Sons, Inc., Hoboken, New Jersey
Published simultaneously in Canada

Library of Congress Cataloging-in-Publication Data:
Crowson, A. Neil.
The melanocytic proliferations : a comprehensive textbook of pigmented lesions / A. Neil Crowson, Cynthia M. Magro, Martin C. Mihm, Jr. – 2nd ed.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-0-470-56155-3 (hardback : alk. paper) – ISBN 978-1-118-48893-5 – ISBN 978-1-118-48894-2 (mobi) – ISBN 978-1-118-48895-9 (pdf) – ISBN 978-1-118-48896-6 (pub)
I. Magro, Cynthia M. II. Mihm, Martin C., 1934– III. Title.
[DNLM: 1. Melanoma. 2. Skin Neoplasms. 3. Melanocytes–pathology. 4. Nevus. WR 500]
RC280.M37
616.99'477–dc23
2013007100

Cover image: iStock file #8099914 © DPhoto
Cover design by Matt Kuhns

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

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Dedication

This book is respectfully dedicated to the memory of Doctor Ramzi Cotran, to those like him who have died or will die from melanoma, and to the men and women who toil to lift this scourge from the brow of mankind.

Preface

Much has occurred in the field of molecular biology since the first edition of this book was published in 2001. Ruifeng Guo, MD, PhD, a resident in the Pathology Department of the University of Oklahoma, has made an important contribution in revising the chapter on biology in this edition. Only as these technologies are applied in the clinical arena are we finding discordance between genomic hybridization and fluorescence in situ hybridization studies on the one hand and morphology and biologic behavior on the other. To our surprise, morphology frequently seems to hold the trump card in predicting behavior. Our suspicions regarding the molecular biopsy of melanoma are two-fold: first, that melanoma is plastic from a molecular perspective, and that the genome of the cancer cell is in flux during disease evolution; and second, that a revolution in the treatment of metastatic melanoma must be based upon a more comprehensive understanding of the afore-stated molecular biology. We believe that histomorphology will continue to be the cornerstone of diagnosis and management for the foreseeable future.

Confocal microscopy has emerged, and the use of dermoscopy has become widespread, in the last decade. Accordingly, we include two new chapters to address these important areas. The former chapter was written by Dr R Condon Hughes of the Diagnostic Tissue/Cytology Group of Meridian, MS, and by Christi Alessi-Fox, Director of Clinical Activities for Lucid Technologies in Rochester, NY. Mitchell A. Kline MD, Clinical Assistant Professor of Dermatology at Cornell University Medical College Weill NY-Presbyterian Medical Center has written the chapter on dermoscopy with the assistance of Jennifer Ostroff, BA. Dr Kline provides an exhaustive atlas of vignettes available through a web-based application open to those who have purchased this textbook. We are indebted to our co-authors for these contributions.

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Disclosure

Dr Cynthia Magro is a co-founder of CEPbiotech, a company with exclusive license to distribute anti-sAC antibodies.

About the Companion Website

This book is accompanied by a companion website:

www.wiley.com/go/crowson/melanocyticproliferations

The website includes:

- Case vignettes

Chapter 1
An Approach to the Clinical Diagnosis of Melanoma, Its Precursors, and Its Clinical Mimics

Introduction

Before the 1960s, melanoma was considered a single, monotypic disease with an ominous prognosis. It was during this decade that systematic study of patients with melanoma first began at the Massachusetts General Hospital (MGH) in Boston, Massachusetts, and at the Royal Prince Alfred Hospital in Sydney, Australia. The opportunity to systematically analyze large patient series flowed directly from the establishment of focused multidisciplinary clinics, of which the seminal example is the Pigmented Lesion Clinic of Massachusetts General Hospital founded by Drs Wallace H. Clark, Thomas B. Fitzpatrick, Martin C. Mihm, Jr, and John W. Raker on April 6, 1966. A primary goal of this clinic was to emphasize clinical diagnosis and to correlate clinical findings directly to histopathology. It was thus that Dr Fitzpatrick was first able to recognize the implication of, and to draw attention to, variegations in the color and border morphology of melanocytic neoplasms (Fitzpatrick and Clark, 1964). As a direct result of these clinical and histopathologic studies, melanoma was shown to be a disease with several distinct subtypes (Clark et al., 1969; McGovern, 1970). Features of early diagnosis gleaned from systematic analytic methods were published in an atlas of pigmented lesions (Mihm et al., 1973) that was widely distributed. The formation of the Melanoma Clinical Cooperative Group, which included the Pigmented Lesion Clinic at the Massachusetts General Hospital and the subsequently formed pigmented lesion clinics of New York University, Temple University in Philadelphia, and the University of California at San Francisco, led to fruitful clinical, epidemiologic, pathologic, and prognostic studies of nevi and of melanoma and its precursors. Among the many contributions that came out of this group effort was an appreciation of the diagnostic features by the clinical practitioner, as encompassed by the mnemonic: "A, B, C, and Ds" of melanoma diagnosis (Friedman et al., 1985), as well as:

1. The addition of acral lentiginous melanoma to the classification scheme.
2. The studies that led to the recognition of a variety of clinical and pathologic factors in prognosis based on multivariate analysis of a variety of different attributes.
3. The recognition of microscopic satellites as a prognostic factor and as a predictor of microscopic deposits of melanoma in clinically negative draining lymph nodes.
4. The recognition, at the University of Pennsylvania Pigmented Lesion Clinic, of the dysplastic nevus and of familial clusters that expressed both multiple dysplastic nevi and melanoma.

The references for this chapter cite merely a fraction of the published contributions that flowed from the many studies that subsequently came from a group led by Drs. T. B. Fitzpatrick, W. H. Clark, A. W. Kopf, S. Blois, and A. J. Sober, who directed the effort for 6 years at their institutions, and their teams of dermatologists, surgeons, oncologists, epidemiologists, statisticians, pathologists, and basic scientists (Day et al., 1982a–d, 1983; Harrist et al., 1984). Pigmented lesion clinics are now active in many centers in the United States and throughout the world, coordinating the scientific study of this complex and deadly neoplasm, its precursors, its epidemiologic features, its treatment and basic research into its biology. With respect to the latter, recognition of a heredofamilial basis for some cases of melanoma and its precursors was a key event in the history of clinical oncology and one that led indirectly to the Human Genome Project, which will, ultimately, have the most profound impact on medicine and the science of human genomics.

Incidence and risk

The remarkable increase in the incidence of melanoma has led to increased interest in the disease from diagnostic, management, and basic science perspectives. In 1935

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Companion Website: www.wiley.com/go/crowson/melanocyticproliferations.

the risk of developing melanoma in the United States was roughly 1 in 1500. The risk is closer to 1 in 87 in the modern era. This is a worldwide phenomenon (Pizzaro Redondo et al., 1998).

Analysis of the risk of developing melanoma helps to identify those individuals who must be more closely examined and followed. One of the most important risk factors is the presence of a changing mole, which is associated with a higher probability of melanoma, emphasizing the importance of self-examination so as to facilitate prompt presentation to a physician for evaluation. Certainly, the presence of many nevi is in itself a risk factor and necessitates follow-up. The risk associated with dysplastic nevi rises according to the number of dysplastic nevi present in a given patient, the presence of a prior melanoma, and a family history of dysplastic nevi and melanoma. A patient who has multiple dysplastic nevi, a prior history of melanoma, and a family history of melanoma may have a risk several hundredfold higher than a person without these characteristics. Siblings with dysplastic nevi in the setting of familial melanoma have a very high lifetime risk of developing melanoma if another sibling similarly affected develops melanoma (Greene et al., 1985). A person with a single dysplastic nevus without any history of melanoma in the family may have a several-fold increased risk of melanoma compared with someone who has no dysplastic nevi. In contrast, a history of sun sensitivity or multiple blistering sunburns does not, in isolation, confer more than a three- or four-fold increase in risk compared with persons without these factors. Risk has been discussed by several authors in several series and varies according to the series (Lewis and Johnson, 1968; Rhodes and Melski, 1982; Doherty and MacKie, 1986; Rhodes et al., 1987; Rigel et al., 1988, 1989; Garbe et al., 1989; Grob et al., 1990; Rhodes, 1994). The striking variation in the number of melanomas associated with nevi deserves comment. Series have been reported with incidences varying from 15% to 85% (Stadler and Garbe, 1990; Elder et al., 1981). In patients with dysplastic nevi, as many as 70% or more of melanomas arise in association with precursor dysplastic nevi (Elder et al., 1981). A striking association between plantar nevi and melanoma was observed decades ago (Lewis and Johnson, 1968).

The issue of sun exposure as it impacts melanoma risk is both intriguing and controversial. First, one must realize that there are different skin types with markedly different responses to sunlight that impact photoaging or "dermatoheliosis." Skin types can be classified according to skin color and, more specifically, according to the response of buttock skin to short sun exposure. The first group comprises roughly 1.5 billion people with pure white, white, and beige skin. These patients are divided into so-called phototypes. Phototype I skin in response to short periods of sun exposure exhibits tender sunburn and does not tan. Phototype II exhibits a tender sunburn and tans only minimally and with difficulty. Phototype III shows nontender sunburn and tans uniformly to a light brown color. Type IV skin, which exhibits a light brown color in non-sun-exposed areas, manifests a minimal sunburn and tans well to a moderate brown color. Patients with brown skin are designated as type V. Their skin rarely burns and tans profusely to a dark brown color. Those patients with black skin are considered type VI and also exhibit no sunburn and a dark tan. Patients with phototypes I and II skin are the most sensitive and are at relatively higher risk of developing melanoma than are the other phototypes (Fitzpatrick TB, *Soleil et peau*, as cited in Barnhill et al., 1995; Pathak and Fitzpatrick, 1993). Despite the interest in sun exposure and melanoma, the question is still open to debate. One interesting aspect of the sun exposure story is that it appears that intermittent recreational exposure places a person at greater risk for developing melanoma than prolonged sun exposure. However, the complexity of the nature of sun exposure, including the impact of different latitudes, different types of sun exposure, and other different patient risk factors, makes the entire issue difficult to resolve clearly (Armstrong, 1988; Gallagher et al., 1989; International Agency for Research on Cancer, 1990; Autier, 1994).

Precursors to melanoma

From the above discussion of risk, it is clear that nevi are one of the precursors of this disease. Certainly, the fact that even an increased number of small nevi can be associated with increased risk implies that even the common acquired nevus can be imputed as a potential precursor, as are the dysplastic nevi or large atypical moles. Lynch et al. (1978) gave the latter appellation to the lesion as part of the "familial atypical mole syndrome". In addition, the congenital melanocytic nevus has been associated with the development of melanoma and thus documented as a cause of death in children (Trozak et al., 1975). Malignant transformation of a cellular blue nevus has rarely been reported. This extremely rare eventuation occurs in a morbidly growing nodule that often ulcerates at the site of a pre-existing, usually nodular cellular blue nevus (Connelly and Smith, 1991).

We also consider lentigo maligna as a precursor of invasive melanoma. The actual incidence of malignant transformation has been disputed, mainly because most series of lentigo maligna melanoma were biased by the nature of patients referred to tumor centers. However, one assessment put the lifetime risk of developing invasive melanoma in lentigo maligna at 2.2–4.7%, depending on the age of the patient at the time of initial clinical appearance of the lesion (Weinstock and Sober, 1987). Other

lesions considered to be precursors, but with a much lower relative frequency of malignant transformation, are the nevus of Ota and the nevus of Ito, the nevus spilus, and the spindle and epithelioid cell nevus (Alegre and Aliaga, 1989; Rhodes, 1994; Williams and Pennella, 1994; Clark et al., 1995; MacKie, 1995; Ruiz-Maldonado and Orozco-Covarrubias, 1997).

Approach to the patient

Initial encounter

There are two case scenarios whereby a pigmented lesion may come to the attention of the examining physician. The first occurs when the patient presents to the physician with a concern regarding a pigmented lesion. The second is when a physician in the course of a routine examination discovers a pigmented lesion that raises his or her suspicion or curiosity. In either scenario, the underlying basic message to physicians is that a patient who comes in for a specific pigmented lesion and/or a routine general examination should be disrobed and a complete skin examination should be performed. The physician must always offer the patient the opportunity to refuse, and if he/she does, this should be documented in the patient's chart. This practice is one that is exercised by all pigmented lesion clinics in the United States and many centers throughout the world. We regard this as a medicolegal imperative. Dermatology residents are instructed to perform complete examinations at the time of initial visit regardless of the presenting complaint.

History

Critical in the historical evaluation is a determination of the duration of the lesion in question and any symptomatology associated with it, such as pain or other sensations such as pruritus, and any history of change in color, size, or shape, all of which should be documented. The findings of oozing, crusting, and bleeding are all significant and are usually late signs. It should also be established whether there has been any prior trauma or surgery to the lesion. A sunburn history should be obtained; such patients appear to have some increased susceptibility to skin cancer and have very sensitive skin in most instances. This piece of information is helpful in assessing the skin type of the patient. In addition, recent sunburn may produce a histomorphology that may mimic a high-grade melanocytic dysplasia when in fact the proliferation represents a chronic or subacute photoadaptive alteration. In women and girls, an alteration of the hormonal status should be investigated, be it in the context of pregnancy or the use of exogenous hormones. The exposure of the skin to plant products in cosmetics, or to droplets of fruit juices such as lime juice, in concert with intense sun exposure, can produce a pigmented lesion with melanocyte hyperplasia, termed a *phytophotodermatitis*, with a most worrisome clinical and histologic appearance. Immunosuppressive therapy and/or chemotherapy may also contribute to the clinical course and light microscopic appearance of the pigmented lesion and hence a history regarding the aforesaid should be obtained. A review of the patient's personal history of skin disease is necessary. In cases where skin lesions have been removed, it is advisable to have available the laboratory reports, especially if the patient reports that he/she has had "skin cancer." Also critical to the clinical assessment is the family history of melanoma, atypical moles, or skin cancer (Barnhill et al., 1995).

Physical examination

The complete examination should be carried out in a well-lit room. We highly recommend that a nurse be in attendance for all complete cutaneous examinations. The patient must be examined anteriorly and posteriorly to detect the number and distribution of pigmented lesions. By this examination, one can assess the skin characteristics of the patient and also the mole phenotype. The hair coloration is helpful in this regard. A basic estimate of the number of nevi and the assessment of the presence of multiple atypical moles can be easily carried out in this way (Barnhill et al., 1995). It is imperative to follow this general examination with a more detailed and comprehensive skin assessment. This examination should include the scalp, glabrous skin, axillae, inframammary folds, umbilicus, genitalia including the intergluteal or natal cleft, palms and soles, and the interdigital areas and nails, focusing on the detection of clinically suspicious lesions. Scalp examination can be facilitated with the use of a hair dryer or a pair of cotton-tipped applicators to separate the hairs. Examination of the face should include the conjunctiva, mouth, and postauricular skin. The use of side lighting may be helpful in evaluating whether a lesion is raised, and a Wood's light can be very helpful to detect haloes of hypopigmentation or areas of partial regression in a lesion. The use of a magnifying lens can be an important clinical diagnostic adjunct. Similarly, the technique of epiluminescence can be helpful, but should only be carried out by physicians familiar with this technique.

For many years, magnification has been used to allow for better inspection of clinical lesions and thus as an aid to diagnosis. As cited by Gilje et al. (1958), J.C. Kolhaus in 1663 used magnification to study the vessels of the nailfold. Saphier was among the very first to use magnification under the title dermatoscopy in 1920 and published a series of seminal observations concerning its application (Saphier, 1920, 1921a–c)). Dr Thomas Fitzpatrick in the late 1960s began to use a fixed binocular microscope to study skin lesions, especially melanocytic lesions. Professor Rona MacKie (1971) reported on the usefulness of magnification in evaluating pigmented

lesions in 1971. One of the difficulties in assessing the pattern of skin lesions is the scattering of incident light by the skin surface components. The application of mineral oil to the skin greatly reduces the light scattering and allows for a better viewing of the clinical features in their three-dimensional aspect. Also, one can appreciate some of the features of the deeper aspects of the lesions. Thus, patterns created by the various cutaneous structures and their infiltration by pigmented cells can be observed and formulated. This technique is given several names, among them epiluminescence microscopy (ELM), dermoscopy, and dermatoscopy (Steiner et al., 1987, 1993; Braun-Falco et al., 1990; Kenet et al., 1993; Pehamberger et al., 1993; Soyer and Kerl, 1993; Stolz et al., 1994; Binder et al., 1994; Wolff et al., 1994; Barnhill et al., 1995; Binder et al., 1995, 1997; Argenyi, 1997; Kittler et al., 1998; Carli et al., 2000). With the application of ELM the presence of a diffuse, delicate network of pigment can be seen to characterize benign melanocytic lesions. The darker areas represent pigmentation of the rete ridges and the lighter areas the dermal papillae. Areas of pale interruption of the pattern resulting in a patchy multifocal appearance of the network are observed in many dysplastic nevi. In contrast, melanomas are found to have multiple components, including a coarse network pattern, a nodular pattern, and border changes. The latter include a pseudopod-like appearance, evidence of the radial growth phase, very sharp network margins, and a whitish or blue–gray veil (Steiner et al., 1987; Kenet et al., 1993; Pehamberger et al., 1993; Barnhill et al., 1995). In our hands we estimate that we remove approximately 30% fewer pigmented lesions than before the use of the dermatoscope as an aid in clinical diagnosis. When combined with conventional clinical analysis, dermoscopy enhances the accuracy of prediction of melanoma thickness (Argenziano et al., 1999). It is important to note that this technique is best used after a training period. It is clear that the application of dermoscopy by the untrained physician can result in increased errors in diagnosis (Binder et al., 1995, 1997). On the other hand, when used in conjunction with conventional clinical examination, dermoscopy may enhance the diagnostic accuracy of the less experienced clinician (Argenziano et al., 1998).

Computerized analysis of pigmented lesions has been a focus of study by many groups. This type of assisted diagnosis is useful according to some studies but is costly and time consuming. However, in the hands of persons experienced in the technique, it can be a useful adjunct to diagnosis (Seidenari et al., 1998, 1999; Landau et al., 1999). Typically, accuracy rates rise by 5% when trained dermatologists use computer-assisted videomicroscopy to augment their clinical acumen (Landau et al., 1999).

In general, those pigmented lesions that are round or oval in shape, have regular borders, and are uniformly pigmented with a size no greater than 5 millimeters are not considered suspicious and therefore do not warrant removal. Such a lesion should only be removed for two reasons: the patient requests its removal for cosmetic reasons or desires it because it is of personal concern. We routinely remove, at the patient's request, lesions that appear to us clinically benign. However, we have all encountered cases of melanoma in which the patient's request for removal of a lesion was declined by the physician because of its benign appearance and that same patient presented at a later date with metastatic disease. Listen to the patient.

Lesions that are greater than 5 mm have a limited differential diagnosis. If flat, they may be congenital nevi, congenital lentigines including a café-au-lait spot, ink spot lentigo, nevus spilus, genital melanosis, or pigmented spindle cell nevus of Reed. Many of these lesions usually have a characteristic clinical picture and do not require excision unless there is a reported area of abnormal pigmentation. The dysplastic nevus, if solitary, should be removed for histologic confirmation. If the patient has multiple dysplastic nevi, only those showing significant atypia or reported to have manifested a change in size, shape, or color should be removed. Solar lentigo, superficial pigmented actinic keratosis, clonal seborrheic keratosis, de novo intraepidermal melanocytic dysplasia, lentigo maligna, or other forms of melanoma in situ are sometimes clinically indistinguishable and therefore must be biopsied or removed in their entirety. Lesions that are greater than 5 mm and raised include the congenital nevus, compound dysplastic nevus, blue nevus, cellular blue nevus, deep penetrating nevus, combined nevus, Spitz nevus, pigmented spindle cell nevus of Reed, atypical Spitz tumor, and melanoma and its borderline variants. The clinical index of suspicion for these lesions must be high, and if there is any doubt about the nature of any given lesion, it should be removed.

Approach to the individual pigmented lesion

A useful mnemonic is the so-called "ABCDEs" of clinical pigmented lesions (Friedman et al., 1985; Stolz et al., 1994).

"A" refers to asymmetry. Atypical pigmented lesions are usually asymmetrical. This description particularly applies to lesions of dysplastic nevus, lentigo maligna, lentigo maligna melanoma, superficial spreading melanoma, and acral lentiginous melanoma. However, some benign pigmented lesions are also asymmetrical, such as the Albright pigmented macule, nevus spilus, and the ink spot lentigo. Conversely, not all symmetrical melanocytic proliferations are benign. Specifically, nodular melanomas or minimal deviation melanomas are usually symmetrical lesions that are expansile, round growths. They require evaluation of other parameters, which will be alluded to presently.

"B" refers to border. The borders of most dysplastic melanocytic proliferations, be they in the context of a dysplastic nevus or melanoma, are irregular. The radial growth phase components of the various types of melanoma all have highly irregular borders. In general, the greater the degree of border irregularity, the greater is the degree of melanocytic atypia. An important aspect of borders of melanomas is that irregularity includes notching, indentation, and irregular convolution. The actual border itself may be pronounced or exaggerated because of induration and/or color prominence, the latter typically reflecting either excessive melanophage accumulation or accelerated tumor growth in the lateral edge. However, in a minority of cases, lesions manifesting irregular borders may be benign, such as the Albright melanotic macule, the solar lentigo, the ink spot lentigo, and the nevus spilus.

"C" refers to color. The colors of melanoma are highly variable within a given lesion. The radial growth phase of superficial spreading melanoma demonstrates the most striking variation in color, whereby a given lesion may exhibit hues of red, white, blue, brown, black, and gray. The colors of radial growth phase lentigo maligna melanoma, acral lentiginous melanoma, and mucosal melanoma show a similarly striking variegated coloration; however, the colors are mainly limited to shades of brown, gray, and black. Areas of white, blue, or gray signify foci of regression and may appear in all the radial growth phases. In vertical growth phase melanoma, the colors of the excrescence may be black, purple, reddish-brown, gray, or amelanotic, the latter imparting a pinkish-white hue. Pure vertical growth phase melanoma, or nodular melanoma, presents as a single, rapidly appearing growth of the skin. Because of the clinical similarity to a hemangioma/pyogenic granuloma and a blue nevus, we recommend the prompt removal of any such colored lesion of recent onset. History is often helpful in distinguishing, for example, a blue nevus present from childhood from a recently appearing, rapidly growing nodular melanoma. Irregularities in color pattern can be observed in benign lesions; however, they are usually "regular irregularities." For example, congenital nevi have a regular pattern of hyperpigmentation around follicular orifices. Likewise, nevus spilus often shows a reticulated pattern of darker pigmentation on a pale brown background. Dysplastic nevi can manifest irregularity in pigmentation, but the colors are primarily in the brown color range. Melanomas, on the other hand, show an irregular, haphazard pattern of coloration and include greater shade ranges, including red, purple, and black, the latter resulting in a dramatic clinical presentation.

"D" is for diameter. In general, most benign common acquired nevi have a diameter no greater than 4 or 5 mm. As discussed above, there is a rather extensive differential diagnosis for lesions greater than 5 mm that includes certain benign lesions. However, careful consideration to complete removal must be given to any lesion of an increased diameter that manifests any of the other A, B, C, or E features.

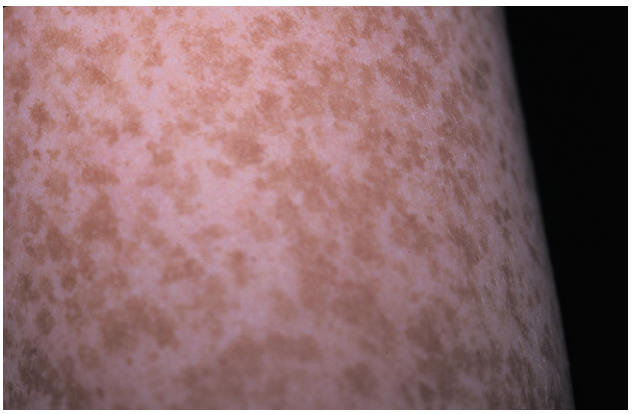
"E" is for elevation. Many melanomas show surface irregularities with asymmetrical foci of palpable nodularity. The radial growth of the lentiginous melanomas is more commonly flat. Rarely, a deeply invasive acral lentiginous melanoma may be flat because of its proliferation from eccrine ducts into the surrounding dermis and subcutaneous fat. Benign lesions are typically uniformly and/or symmetrically elevated.

Summary

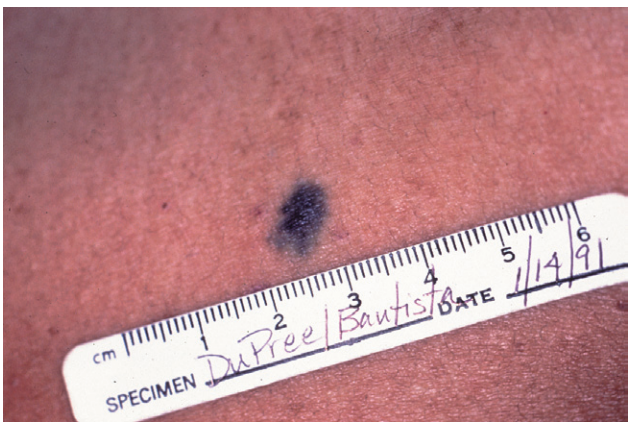
A complete evaluation of the patient must be systematically performed, and any pigmented lesions should be evaluated according to the "ABCDE" rules given above. Any suspicious lesion must be biopsied or removed in its entirely. It is our consummate recommendation that any lesion that is suspicious enough to be removed be excised rather than biopsied. A partial biopsy of a lesion can often result in an incorrect diagnosis because the area chosen, although perhaps clinically most suspicious, may not be representative of the most biologically aggressive portion of the lesion. The classic case scenario is a biopsy procured from an area of regressed radial growth phase-confined melanoma that produces a histomorphology cognate to a benign lichenoid keratosis. In fact, we suggest that any clinically suspicious pigmented lesion that is biopsied and whereby such a diagnosis is rendered pathologically should be removed in its entirety for full histologic evaluation. The only setting in which we recommend a biopsy is where the lesion is so large that complete removal is not practical for initial evaluation, e.g., a large lesion of lentigo maligna or solar lentigo. In intermediate-sized and giant congenital nevi or lesions of nevus spilus, it is likely that biopsies from abnormal areas only are warranted. We will now present clinical examples of specific lesions that are discussed in detail in the text that follows.

ATLAS OF CLINICAL LESIONS CORRELATING TO VARIOUS ENTITIES DISCUSSED IN THE TEXT

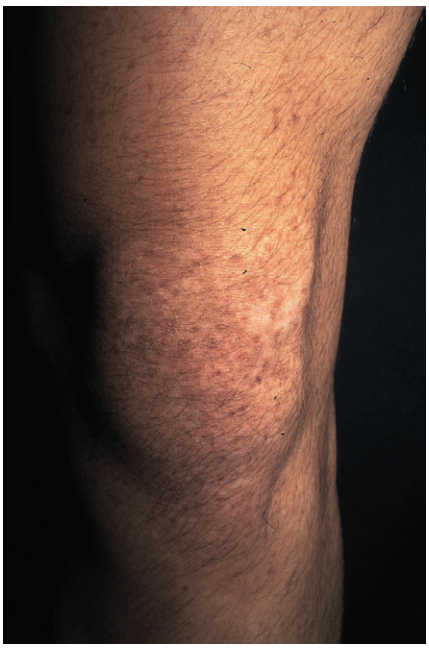
Chapter 2: Freckles and Lentigines



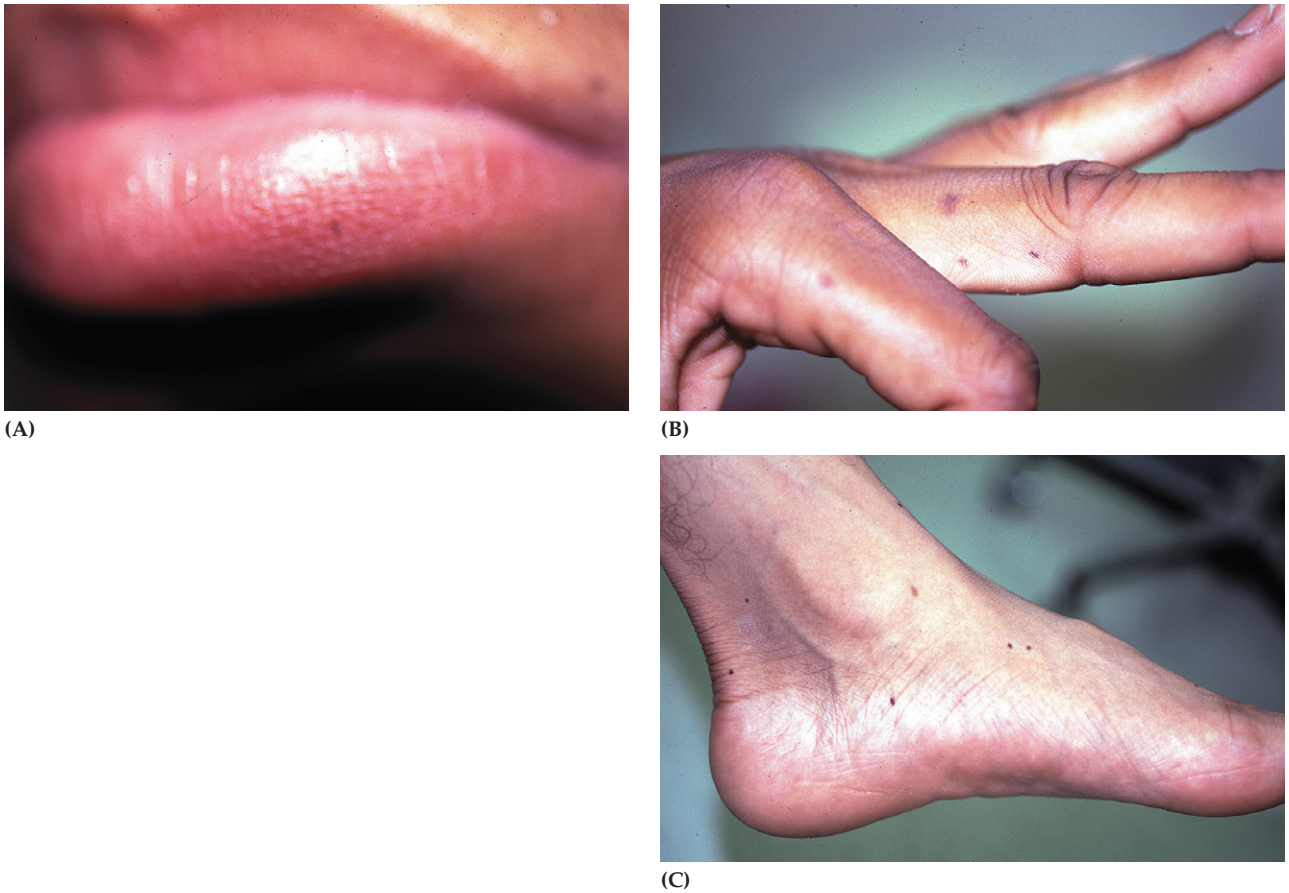
Atlas Figure 2.1 Freckle. Freckles manifest as multiple tan macules typically in the 2–4-mm size range, some with irregular borders but none with irregular pigmentation, that characteristically fade in the winter to reappear in the summer. This sun-related behavior helps to differentiate them from other flat pigmented lesions.



Atlas Figure 2.2 Lentigo simplex. The typical appearance is that of an oval 2–3-mm lesion that is light tan to dark brown. Although common in childhood, these lesions may appear at any time in life, do not evolve, and may affect any surface, including those of the mucosae. (Courtesy of Dr M. DuPree, Albany, NY.)

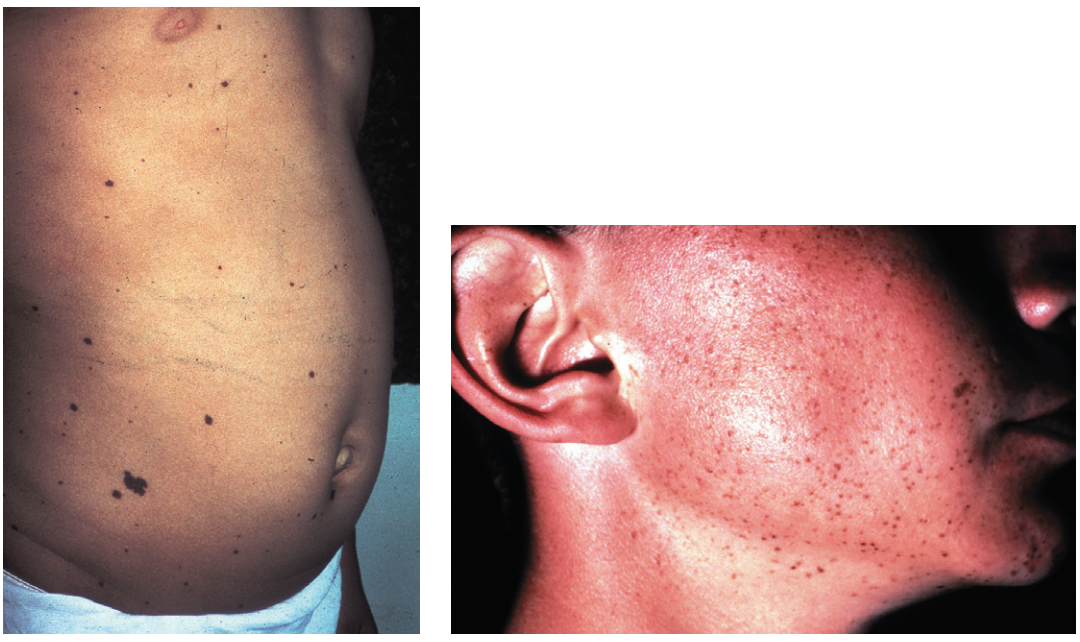


Atlas Figure 2.3 Acral reticulated pigmentation of Kitamura. A diffuse, reticulated pigmentation of the extremities with occasional involvement of the trunk characterizes this variant of lentiginosis.



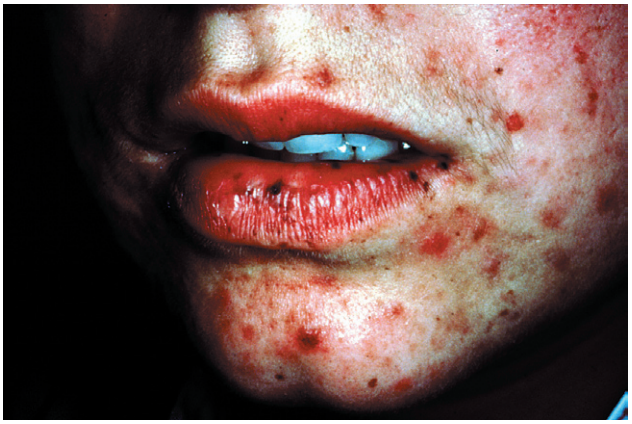
(A) **(B)** **(C)**

Atlas Figure 2.4 (**A**–**C**) Lentiginosis of Laugier–Hunziker. Multiple lentigines of the lips, sides of the fingers, and feet characterize this disorder that is often confused with Peutz–Jeghers syndrome. The acral distribution is the distinguishing clinical cutaneous manifestation of the Laugier–Hunziker disorder. This 18-year-old African–American youth was referred for evaluation for Peutz–Jeghers syndrome; after careful dermatologicl examination the correct diagnosis was made.

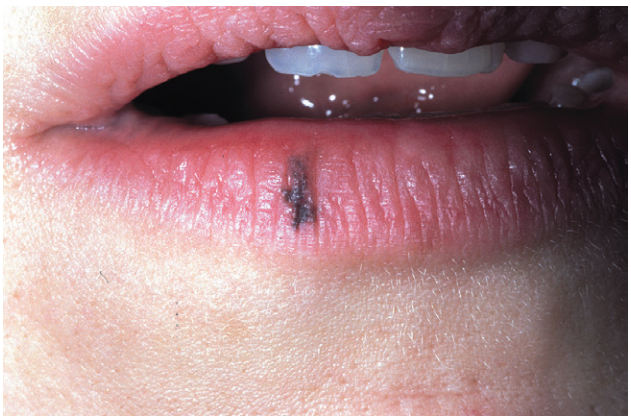


(A) **(B)**

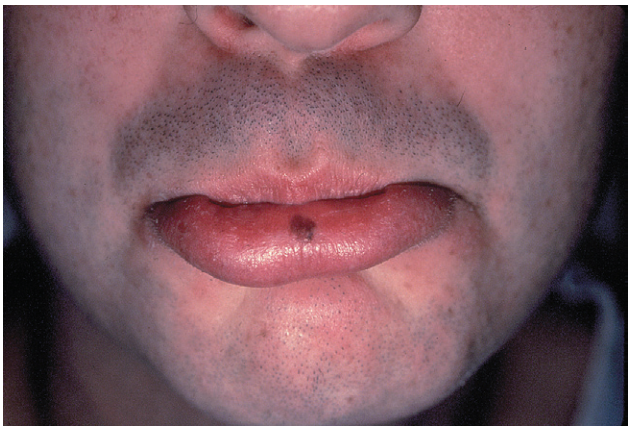
Atlas Figure 2.5 (**A**, **B**) LEOPARD syndrome. Tan to dark brown macules on the trunk characterize the cutaneous manifestations of this 10-year-old boy with LEOPARD syndrome (**A**). Note the multiple punctate pigmented lesions, which represent the characteristic lentigines associated with LEOPARD syndrome (**B**). (**B**, courtesy of Dr M. DuPree, Albany, NY.)



Atlas Figure 2.6 Peutz–Jeghers syndrome. Tan to dark brown macules on the lips and buccal mucosa are the characteristic mucosal and perioral skin manifestations of the syndrome.

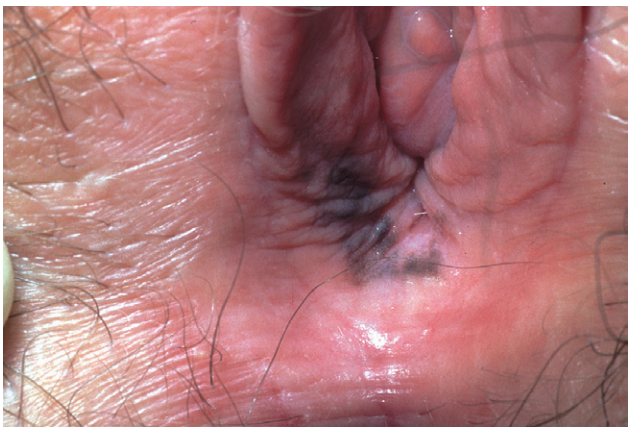


(A)

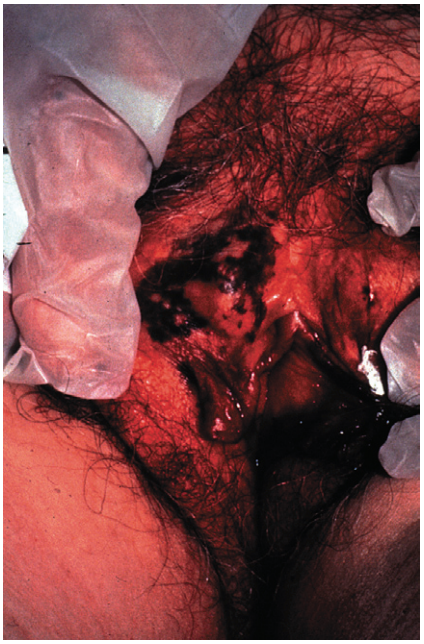


(B)

Atlas Figure 2.7 (**A**, **B**) Labial melanotic macule. (A) A uniformly pigmented dark brown, often symmetrical, lesion is usually found on the lower lip, placed centrally or just off center. Occasionally, these lesions also appear on the upper lip. Lower labial macules tend to be stable and do not evolve. If progressive increase in size or alterations in color are noted, biopsy is recommended to rule out lentigo maligna or a mucosal lentiginous melanoma. (**B**) Shows a lower labial macule present, as is characteristic, in the midportion of the lower lip. (**A**, courtesy of Dr Steven Oberlander, Boston, MA; **B**, courtesy of Dr Anthony Benedetto, Philadelphia, PA.)

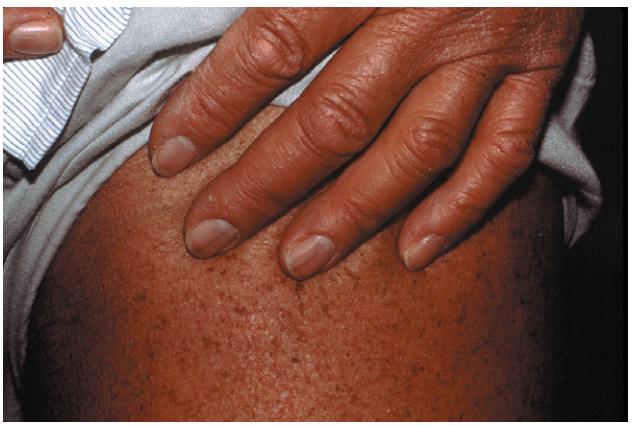


(A)

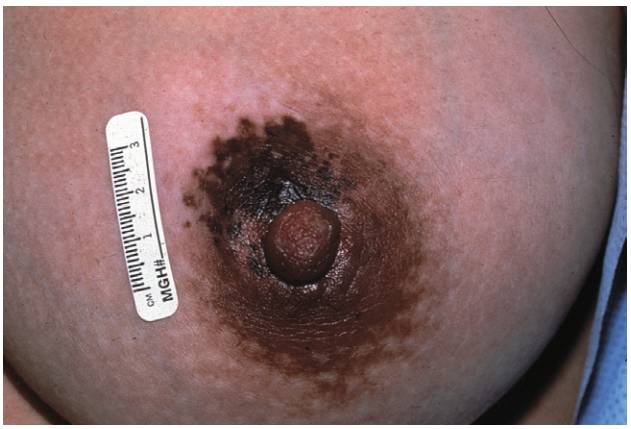


(B)

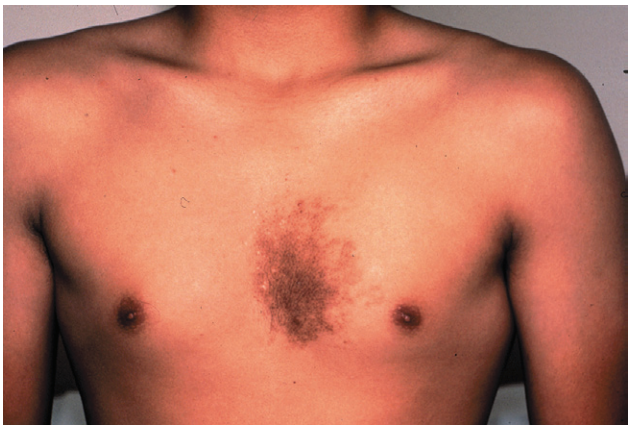
Atlas Figure 2.8 (**A**, **B**) Vulvar melanosis. These lesions characteristically are uniformly tan to brown colored and may affect large areas of the vulvar skin. They must be biopsied to rule out an atypical melanocytic proliferation and should be carefully followed clinically. (**B**) An extensive, darkly pigmented macule extends from the labium majus into the vaginal vault. This lesion is impossible to distinguish from a radial growth phase superficial spreading melanoma on clinical grounds and so must be biopsied. (**A**, courtesy of Dr S. Oberlander, Boston MA; **B**, courtesy of Dr M. Dupree, Albany, NY.)



Atlas Figure 2.9 PUVA lentigines and nail pigmentation. Patients who have received chronic therapy with psoralen and ultraviolet A light often exhibit freckling of the exposed and even nonexposed skin, the latter a well-observed, but as yet unexplained, phenomenon. In this patient, pigmentation of the nails was likewise noted.



(A)



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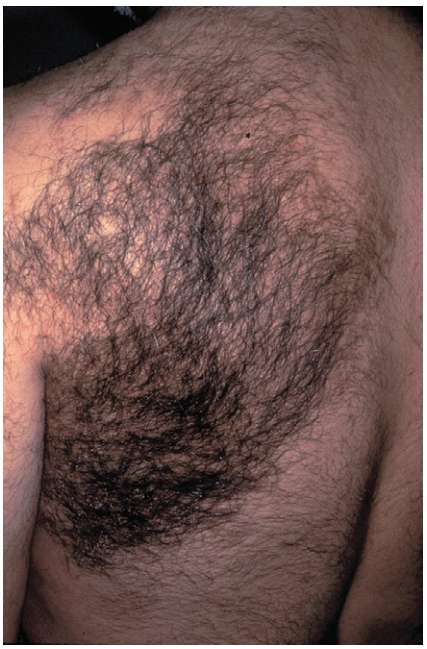
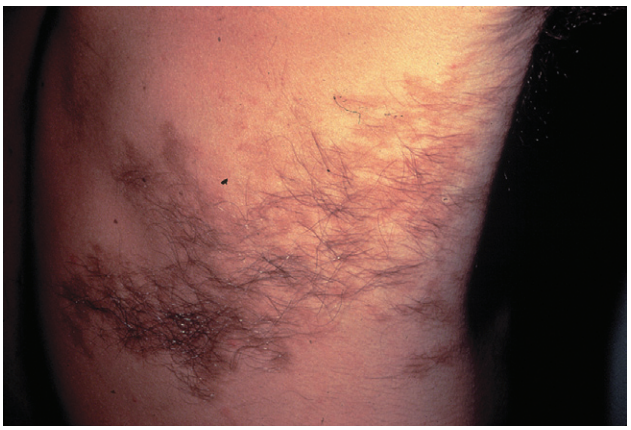
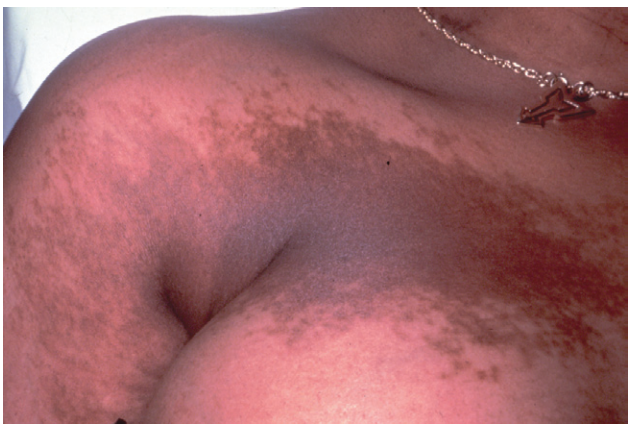


(C)

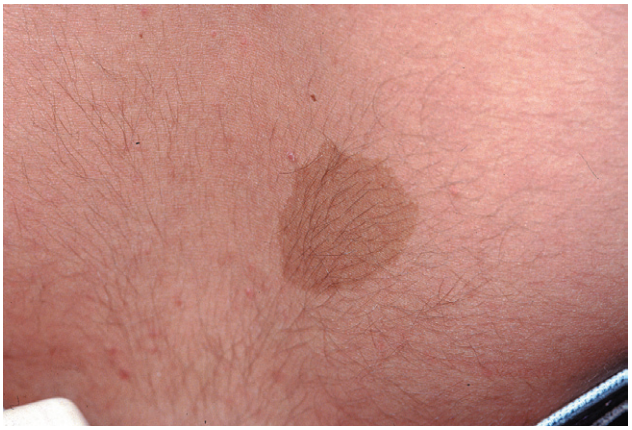


(D)

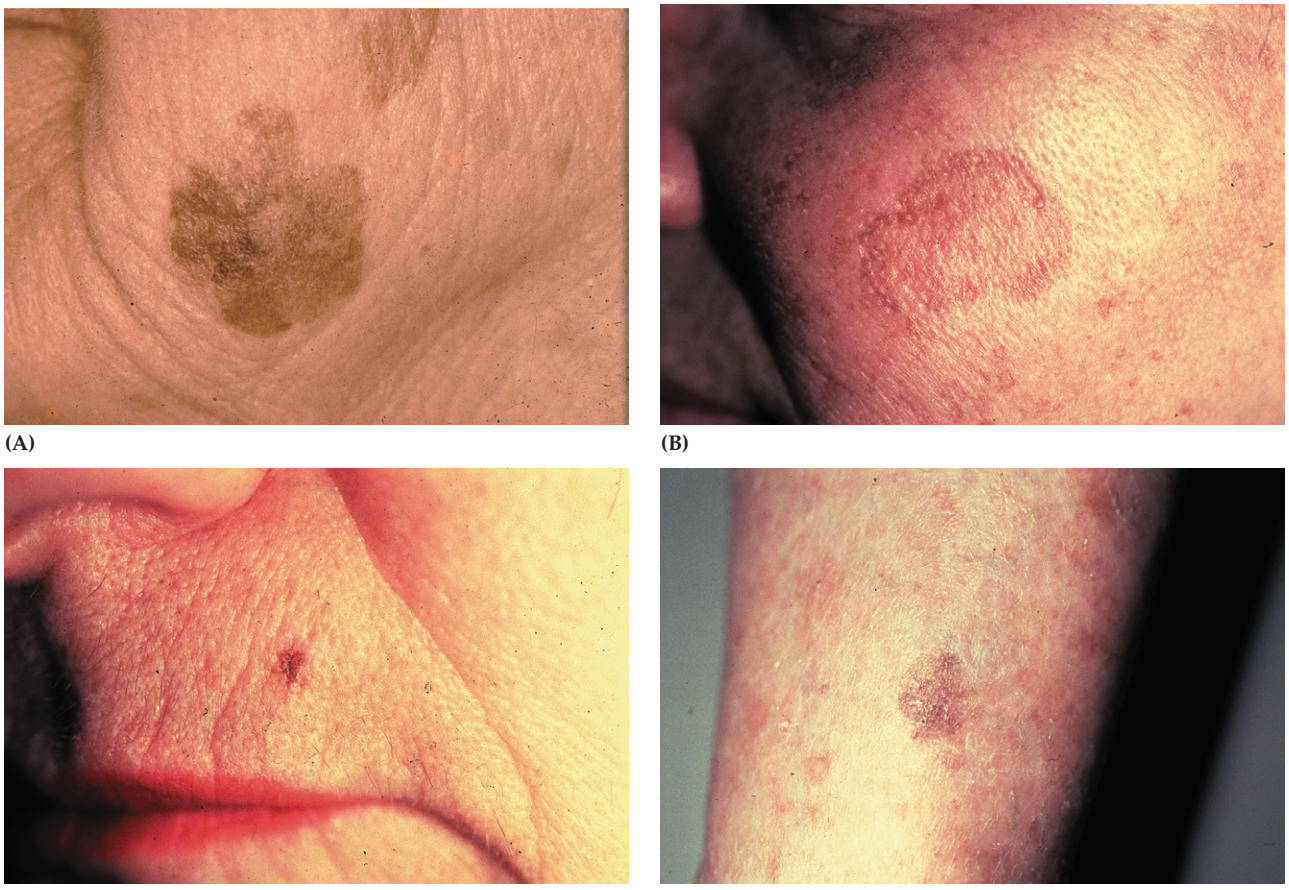


(E)

Atlas Figure 2.10 (**A–E**) Becker's nevus. This pigmented lesion (**A**) with a verrucous surface appeared in late childhood and progressed from the areola to the adjacent skin. The histology was characteristic of Becker's nevus. (**B**) Shows a lesion from the sternal region of an adolescent boy; the lesion has numerous hairs protruding from it, which attest to a follicular component and are a clue to the hamartomatous nature of the lesion and to the diagnosis. (**C**) An example is shown of a Becker's nevus that has a striking hairiness in a characteristic distribution pattern with well-demarcated pigmentation. (**D**) Becker's nevus may present as an extensive, irregularly-disposed lesion on the trunk. As in this lesion, there can be a variable numbers of hairs. (**E**) Demonstrates a giant pigmented Becker's nevus with a plaquelike central zonal coloration and multiple small satellites. It exhibits relatively little hair growth. (**B**, courtesy of Dr M. Dupree of Albany, NY; **C–E**, courtesy of Dr A. Benedetto, Philadelphia, PA.)

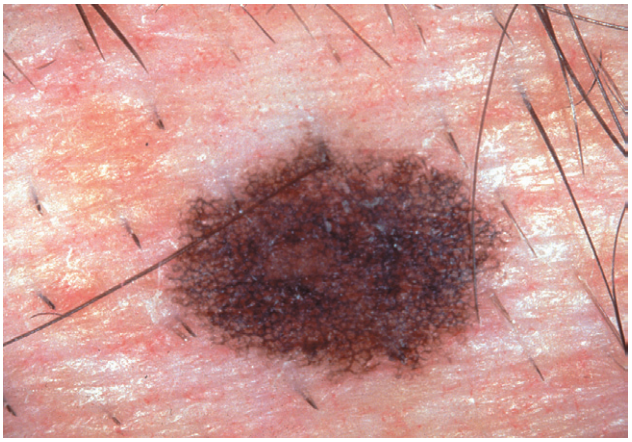


Atlas Figure 2.11 Café-au-lait macule. These lesions have symmetrical shapes with smooth borders and uniform tan pigmentation. They are typically greater than 5 mm in size. When there are more than five such lesions greater than 5 mm in diameter, the presumptive diagnosis is peripheral type I neurofibromatosis.

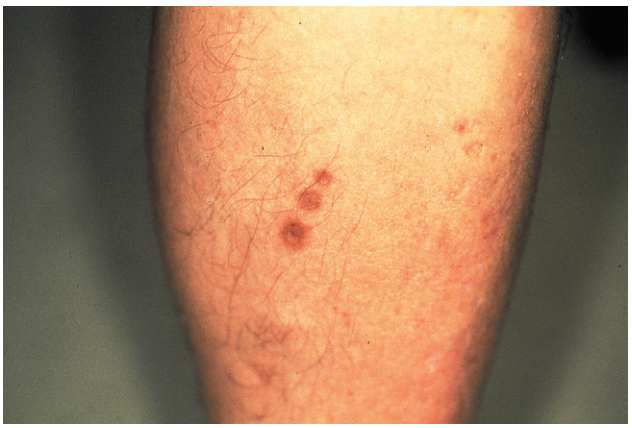


(A) **(B)** **(C)** **(D)**

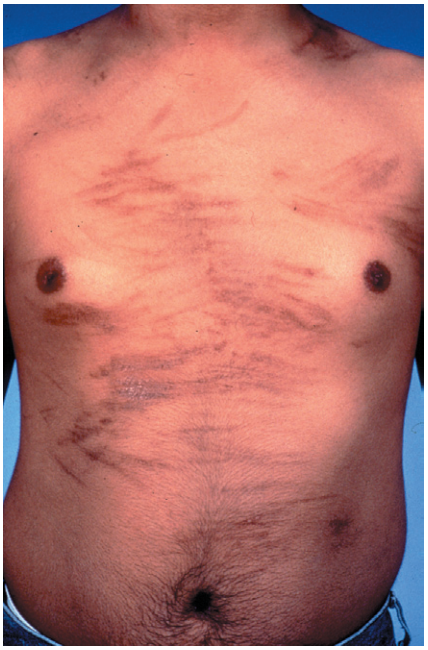
Atlas Figure 2.12 (**A–D**) Solar lentigo. (**A**) This pigmented macular and focally slightly raised lesion suggests, at first glance, a lentigo maligna. However, the presence of a slightly raised area that exhibits discrete flecks of pigmentation and a dull surface speaks strongly for a solar lentigo. Biopsy was performed to confirm the clinical impression. (**B**) This is a solar lentigo that has assumed the size of a few centimeters. They can be very difficult to differentiate from lentigo maligna but usually have less surface reflectance in the adjacent skin and will have some slight scaliness, as in this case. Nevertheless, biopsies of these lesions are recommended to confirm the diagnosis. (**C**) This actinic lentigo is a tan lesion, oval in shape, with the characteristic appearance seen in lesions in sun-exposed skin of an elderly person. In contrast, although simple lentigines can appear at any time in life, they are rare in adults, especially in the elderly, and should be observed or biopsied. (**D**) Demonstrates a coexistent actinic lentigo and superficial pigmented actinic keratosis. This lesion has a dull reflectance compared to adjacent skin and thus can be differentiated from lentigo maligna. (**B–D**, courtesy of Dr A. Benedetto, Philadelphia, PA.)



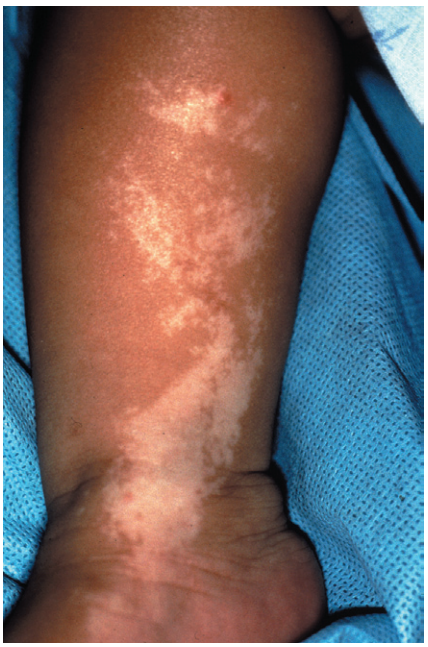
Atlas Figure 2.13 Ink-spot lentigo on right anterior chest. This deeply pigmented reticulated black lesion occurs more characteristically on the upper back of fair-skinned individuals in late adolescence or early adulthood. Men are affected more frequently than women; the lesions are stable but to the uninformed suggest melanoma. The spiderlike extensions are characteristic and helpful in diagnosis. This irregularly-pigmented macular lesion shows the characteristic reticulated pigmentation of the ink spot lentigo. (Courtesy of Dr A. W. Kopf, New York, NY.)



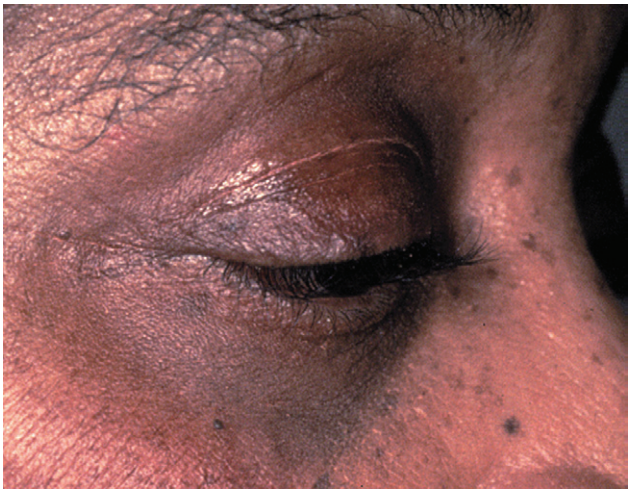
Atlas Figure 2.14 Postinflammatory hyperpigmentation. Postinflammatory hyperpigmentation resulting from a hypersensitivity response to flea bites is punctate in character, often shows a central pustule, and assumes a linear array, reflecting the transit of the insect through "breakfast, lunch, and dinner." For some obscure reason, these lesions often come in threes, of which this would appear to be a classic example. (Courtesy of Dr M. DuPree, Albany, NY.)



Atlas Figure 2.15 Bleomycin hyperpigmentation. The characteristic pattern of pigmentation is in parallel lines suggestive of whip marks, thus the designation "flagellate hyperpigmentation." (Courtesy of Dr M. DuPree, Albany, NY.)

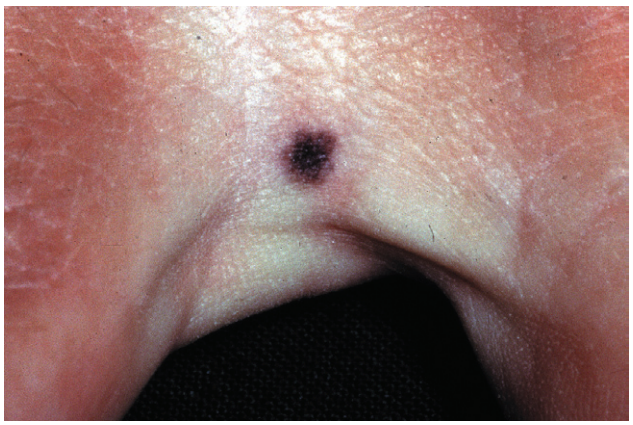


Atlas Figure 2.16 Hypomelanosis of Ito. Note the striking patchy linear hyper- and hypo-melanosis characteristic of hypomelanoma of Ito. (Courtesy of Dr M. DuPree, Albany, NY.)



Atlas Figure 2.17 Melasma, treated. This patchy brown pigmentation surrounding the eye and on the right cheek is characteristic of predominantly epidermal melasma. (Courtesy of Dr A. Benedetto, Philadelphia, PA.)

Chapter 3: Benign Acquired Nevi



Atlas Figure 3.1 Acral junctional nevus. This small, oval, uniformly dark brown lesion is slightly raised and has the characteristic morphology of a junctional nevus. The clinical picture is indistinguishable from that of a junctional nevus in any anatomic location, although the histology may be distinctive. (Courtesy of Dr Mirek Stranc, Winnipeg, MB.)