VITILIGO

A MONOGRAPH ON THE BASIC AND CLINICAL SCIENCE

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This monograph on vitiligo is dedicated to
Dr Taeha Woo, a pioneer for Korean dermatology,
who encouraged, motivated and supported the editors
in the preparation of this book.

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Blackwell Wissenschafts-Verlag GmbH
Kurfürstendamm 57
10707 Berlin, Germany

Blackwell Science KK
MG Kodenmacho Building
7–10 Kodenmacho Nihombashi
Chuo-ku, Tokyo 104, Japan

First published 2000

Set by Excel Typesetters Co.,
Hong Kong
Printed and bound in France
by Imprimerie Pollina, Luçon

A catalogue record for this title
is available from the British Library

ISBN 0-632-05071-3

Library of Congress
Cataloging-in-publication Data

Vitiligo / edited by Seung-kyung
Hann, James Nordlund.
p.; cm.
Includes bibliographical references.
ISBN 0-632-05071-3
1. Vitiligo.
I. Hann, Seung-kyung.
II. Nordlund, James J.
[DNLM: 1. Vitiligo—diagnosis.
2. Vitiligo—etiology.
3. Vitiligo—therapy. WR 265
V844 2000]
RL790. V55 2000
616.5'5—dc21

99-046475

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Contents

Part 5: Topics Related to Vitiligo

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Foreword

Knowing how most victims of vitiligo feel about their disfigurement, and knowing the relationship between vitiligo and disorders of immunity and melanoma, my major goal has been to make vitiligo a 'real disease'. That is, to make it a disorder important to both patients and physicians. Vitiligo is always of major significance to patients who have it, in contrast to the indifference of many physicians. This timely and comprehensive monograph by Drs Hann and Nordlund is of great help. Many aspects of the basic biology of pigment cells, as they relate to vitiligo, are reviewed by 27 authors. The history of vitiligo, the hypotheses of melanocyte destruction, the treatment of patients and many other topics are well covered in this book. For those interested in vitiligo, it is essential to have this book.

More than 20 years ago, I wrote a review article entitled *Vitiligo: What is it? Is it important?* The answer is yes. Vitiligo is important. Knowing more about the processes involved in the destruction of pigment cells as they occur in vitiligo will not only provide us with a method to stop the spread of vitiligo, but also help us to know more about autoimmunity and ways to control melanomas. Vitiligo is a real disease.

Aaaron B. Lerner

Preface

Vitiligo is an enigmatic disorder and thus fascinating to dermatologists, pigment cell biologists and to others who love biology. That the disorder can destroy melanocytes in the interfollicular epidermis, in the eyes, and possibly the ears but spare those melanocytes in the hair follicle is a remarkable phenomenon. Equally bizarre is the observation that vitiligo can be spreading in one area of the integument while melanocytes are proliferating in other areas and repigmenting the skin. How the pathogenic mechanisms can be active in one site while inactive in other sites is puzzling indeed.

Depigmentation is common in the animal kingdom, especially notable in the mammalian species. There are many types of pigment loss, many of which resemble vitiligo and from which we all can learn much about the pigmentary system. It is especially mystifying that melanomas, an uncontrolled proliferation of melanocytes, can be associated with destruction of melanocytes in skin surrounding the cancer or at distal sites, although this type of pigmentary loss might be different from classical vitiligo. And that depigmented halos occur around naevi, angiomata and other cutaneous structures is well known but a phenomenon for which there is no explanation.

This monograph is intended to bring these and related topics into a single repository for dermatologists and other biologists. In addition it is the hope that a review of the pathogenic mechanisms might be a stimulus to others to become interested in and investigate this disorder so prevalent world wide. The chapters on therapy are intended to assist the practitioner in gaining sufficient expertise to care for those with vitiligo but the principles of treating vitiligo should be applicable to many other types of skin disorders as well.

Finally, it is the hope of the editors that this volume can be revised and updated every five years because of the profusion of new information that becomes available from scientists and clinicians from around the world as an indicator that the dermatological world is closer to solving the problem of vitiligo and its treatment.

The editors wish to acknowledge the critical role of their teachers and thank them for being a stimulus for their interest in studying vitiligo and in preparing a monograph on vitiligo. There were special teachers who motivated us to study this disorder, its treatment and other issues related to pigmentation. Drs Taeha Woo and Yoon-Kee Park introduced Dr Hann to the fascination of this mysterious disorder of pigmentation. Dr Aaron Lerner was the inspiration for Dr Nordlund to begin his interest in pigmentation and vitiligo.

We thank all the contributors for their assistance in making this a comprehensive

treatise on the basic and clinical science related to vitiligo and other forms of depigmentation.

Acknowledgements

The editors and authors wish to thank Ms Joan Griggs, Mrs Mary Brocker, Mrs Isook Kim, and Mrs Bobbie Lambert without whose help this volume could not have been completed. Their cheerfulness, dedication and efforts made preparation of this monograph a joy.

PART 1
GENERAL TOPICS ABOUT VITILIGO

1: Definition of Vitiligo

SEUNG-KYUNG HANN AND JAMES J. NORDLUND

The definition of vitiligo

Vitiligo is a specific type of leukoderma manifested characteristically by depigmentation of the epidermis. Occasionally the loss of melanin is partial, i.e. hypopigmentation. Vitiligo is best defined as an acquired, progressive disorder that selectively destroys (or that results in the selective disappearance) of some or all melanocytes residing in the interfollicular epidermis and occasionally in the hair follicles as well. The mechanism(s) by which the melanocytes are lost (or by which melanocytes are made to disappear) may be multiple but is not yet identified unequivocally.

Clinically vitiligo is characterized by white macules on the skin that can be few or many in number. The depigmentation can be localized, moderate in extent or wide spread, even resulting in a complete loss of all interfollicular melanocytes. Very rarely all melanocytes in both the interfollicular and follicular epidermis are destroyed. Such individuals will have entirely white skin and hair.

There are several clinical types of vitiligo. The unilateral (segmental) form usually does not cross the midline and does not have a classical dermatomal distribution but affects one segment of the integument. The segment might be composed of several or parts of several adjacent dermatomes or have no relationship to dermatomes at all. The progression is usually limited to months or a few years (Barona *et al.* 1995; Hann & Lee 1996).

The bilateral (non-segmental) form is characterized by bilateral, usually symmetrical, depigmented macules. It is further subdivided into a localized form (type), limited to small areas of the integument, and into the generalized type. The latter is characterized by widespread extensive depigmentation that most commonly spreads throughout the life of the individual. In addition there is a very rare variety of generalized vitiligo that seems to be a manifestation of a systemic autoimmune disease. This disorder is manifested by vitiligo, as well as multiple endocrine failures such as diabetes mellitus, adrenal insufficiency, thyroid dysfunction and gonadal dysfunction. All of the latter endocrine abnormalities seem to be caused by autoantibodies but the cause of the loss of melanocytes remains unidentified.

Persisting enigmas about vitiligo

Much clinical and basic research on vitiligo has been done and new concepts have been developed. Therefore, a new definition of vitiligo should be made in accordance with the new concepts. In order to make a new definition, some controversies concerning the definition or nomenclature of vitiligo should be discussed.

One very important question is whether vitiligo is only a cutaneous pigmentary disorder or a systemic disorder of the pigmentary system. The pigmentary system of the ears and eyes shows degenerative changes in some patients with vitiligo. Discrete areas of depigmentation, with associated pigment hyperplasia involving the choroid and retinal pigment epithelium as well as active uveitis, have been observed in as many as 40% of patients with vitiligo (Albert *et al.* 1979, 1983). Vitiligo patients exhibit some audiologic abnormalities such as sensorineural hypoacusis, which may be related to involvement of the inner ear melanocytes (Tosti *et al.* 1987). Because most patients with vitiligo who have audiological and ophthalmological changes are usually free of symptoms or have vague complaints, involvement of melanocytes in the extracutaneous parts of the body is easily overlooked. Vogt–Koyanagi–Harada and the Alezzandrini syndromes might be the most severe examples of vitiligo of the skin and the pigment system of the eyes. Most investigators consider the Vogt–Koyanagi–Harada and Alezzandrini syndromes to be different diseases to vitiligo.

A second question is whether chemical depigmentation or occupational depigmentation, which occurs following contact with a phenolic compound or monobenzyl ether of hydroquinone, is in fact vitiligo with a known precipitating cause or some other depigmenting disorder. In our opinion, they are different disorders because chemical and occupational depigmentation tend to be limited to sites of exposure to the melanocytotoxic material. In addition, the clinical course of depigmentation differs. Vitiligo tends to be progressive throughout the life of affected individuals. In contrast, chemical depigmentation usually stops spreading after the offending agent is removed. We propose separating vitiligo vulgaris from chemical and occupational leukoderma until there is definitive data to show the two disorders have a common pathogenesis.

A third question that must be addressed is whether halo naevi are a form of vitiligo. The answer is unknown. Both halo naevi and vitiligo vulgaris are common in children and teenagers. However, there are striking differences between vitiligo and halo naevi. Halo naevi tend to have spontaneous repigmentation. They do not tend to enlarge by centrifugal spread without limit nor do they progress over the whole body. It is our opinion that halo naevi associated with vitiligo are an example of common abnormalities occurring together.

A fourth question that must be addressed is whether grey hair or white hair are a form of vitiligo. Grey hair is the ageing of melanocytes of hair fol-

licles, a process that is associated with interruption of melanogenesis. In contrast, white hair usually means a complete absence of melanocytes from the papilla of the hair follicle. White hair is classified into two types. One is genetic or familial and is a rather common cause of total loss of pigment of the scalp hair in younger adults in the third and fourth decade of life. It is our opinion that this type of depigmentation of the hair is not the same disorder as vitiligo vulgaris and the two forms of depigmentation should be distinguished. The other type of complete white hair of the scalp is uncommon but is associated with vitiligo. White hair is often accompanied by interfollicular depigmentation especially when it is associated with vitiligo. It seems likely that loss of melanocytes in the follicles of those with vitiligo represents the same destructive process active within the hair bulb.

A fifth issue is the association of depigmentation with other disorders. Depigmentation can occur on normal skin or on lesions of patients with malignant melanoma (Koh *et al.* 1983; Nordlund *et al.* 1983). Depigmentation in patients with metastatic melanoma is a surprisingly common and striking phenomenon. It has been suggested that it might represent a good prognostic sign for those with metastatic melanoma (Nordlund *et al.* 1983). The distribution of depigmentation associated with melanoma is different from that of vitiligo. Depigmentation begins as small, round macules which are most prominent on the chest and upper back. It is our opinion that depigmentation associated with melanoma should be distinguished from vitiligo.

In conclusion, vitiligo is a type of leukoderma that should be defined as an acquired, progressive depigmentation with unpredictable course. It classically involves integument and probably affects the pigmentary system of other organs. Other forms of leukoderma should be distinguished from vitiligo until more information is available about their pathogenesis, and these disorders labelled as specific forms of depigmentation such as chemical or occupational depigmentation or depigmentation associated with melanoma.

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2: The Loss of Melanocytes from the Epidermis: the Mechanism for Depigmentation of Vitiligo Vulgaris

JAMES J. NORDLUND

Patients with vitiligo note the loss of colour from their skin when the disorder first begins or spreads. Melanin is synthesized within the melanocytes and later transferred to surrounding keratinocytes. The colour of the skin is determined to a large extent by the amount and type of melanin within the epidermis (Nordlund *et al.* 1998). There are two mechanisms by which the melanin might disappear from the skin and the skin turn white. The first is dysfunction of the melanocytes, the second is loss of the melanocytes themselves. There are many examples of both types of mechanism being involved in various abnormalities of skin colour (Nordlund *et al.* 1998).

Albinism is a disorder characterized by genetic defects that partially or completely impede the synthesis of melanin. The number of melanocytes in the epidermis of an albino is the same as that in a normally pigmented person, only the machinery for the production of melanin is defective. The skin of an albino can have varying amounts of colour, from virtually no melanin (the classical tyrosinase negative albino) to moderate amounts of melanin in all three forms of oculocutaneous albinism (King 1998). Other disorders of hypopigmentation that are caused by a defect in melanin production or transfer include the Chediak–Higashi syndrome, Hermansky–Pudlak syndrome, the Angelman and Prader–Willi syndrome (reviewed in Nordlund *et al.* 1998).

The other mechanism for absence of melanin from the epidermis is a deficiency of melanocytes. Melanocytes can be absent from the epidermis at the time of birth or can be lost later in life. Absence of melanocytes from the epidermis at birth is called piebaldism, a term that means white striped. Such individuals usually have a family history of white macules present from birth. During embryogenesis melanocytes fail to complete their migration from the neural crest to the epidermis (Spritz 1998). As a result there are no melanocytes in the interfollicular or follicular epidermis and the skin and hair are completely white.

In contrast, some individuals acquire white macules on the skin after birth from the condition vitiligo vulgaris. In general most investigators have concluded that the white macules characteristic of vitiligo are a manifestation of loss of melanocytes. There are numerous data upon which this conclusion is based. However, it is not easily proven beyond doubt that melanocytes are absent from the epidermis. A few investigators have recently proposed that melanocytes remain in the skin but become

dysfunctional due to biochemical defects (Schallreuter *et al.* 1994a, b, c).We present here the data which make us conclude that the depigmentation observed in patients with vitiligo is a result of loss of melanocytes from the epidermis.

Histological studies

There have been a number of studies reported in which investigators examined the skin of vitiligo lesions for persistence of melanocytes. Some melanocytes can be found in epidermis of early lesions (Galadari *et al.* 1993) that are only partially depigmented and in which some colour persists. In late lesions that were totally depigmented, there was complete absence of melanocytes by light or electron microscopy (Bleehen 1976; Morohashi *et al.* 1977; Ortonne *et al.* 1979, 1980; Moellmann *et al.* 1982; Galadari *et al.* 1993; Arrunategui *et al.* 1994). These studies have been confirmed by more recent studies in which the investigator utilized a series of fluorescent tagged antibodies directed against a battery of antigens on the surface molecules on melanocytes (Le Poole *et al.* 1993). The antibodies failed to identify mature or immature melanocytes in the depigmented skin from patients with vitiligo. The results of these studies confirm those of prior studies (see Chapter 5).

Melanocyte cultures

Several investigators have noted that the melanocytes from an individual with vitiligo exhibit abnormal behaviour in culture, an indication that the cells are intrinsically abnormal (Puri *et al.* 1987, 1989; Ramaiah *et al.* 1989; Boissy *et al.* 1991a, b). The unidentified abnormality makes the culture of melanocytes from individuals with vitiligo difficult. This problem recently has been solved (Medrano & Nordlund 1990). Using the techniques described by the latter investigators, others have attempted to culture melanocytes from the depigmented patches of vitiligo. The attempts were unsuccessful (R. Boissy, personal communication), a result that supports the absence of melanocytes rather than dedifferentiation or dysfunction of melanocytes.

Response to therapy

Possibly the strongest evidence that melanocytes are, in fact, truly absent from the epidermis in the depigmented skin of vitiligo is the response to medical and surgical therapies. Medical therapies like psoralen with long wavelength ultraviolet light (PUVA) or topically applied steroids presumably rely on pre-existing melanocytes in the follicular apparatus to repigment the skin. The reservoir for melanocytes seems to reside in the hair follicle (reviewed in Nordlund & Ortonne 1998 and Dourmishev *et al.* 1982; Cui *et al.* 1991; Arrunategui *et al.* 1994, see Chapter 20). Glabrous skin which

is, by definition, devoid of hair follicles is found on the palms, soles, tips of the fingers and toes, the genitalia and the lips. It is well known that depigmented patches of vitiligo on glabrous skin do not respond to medical therapies for vitiligo. There should be no difference in response to therapy between the glabrous and nonglabrous skin if melanocytes persisted in the vitiligo patches and the melanocyte reservoir were unnecessary.

It also has been observed that hair-bearing skin in which the hair is white (not grey) also does not respond to medical therapies like PUVA or topically applied steroids. This response is in contrast to skin with pigmented hairs that commonly, although not always, responds to treatments like PUVA (Nordlund & Ortonne 1998) (see Chapter 21). It is common to observe white hairs in segmental vitiligo (personal observation), possibly the reason why segmental vitiligo often is resistant to medical therapies (Koga 1977; Falabella 1983; Behl 1985; Koga & Tango 1988; Ando *et al.* 1993). In addition, results of several studies have demonstrated that when skin does respond to therapy with PUVA or topical steroids, the melanocytes migrate from the hair follicle (Ortonne *et al.* 1979, 1980; Cui *et al.* 1991). That pigmented hairs are required for vitiligo skin to repigment strongly supports the conclusion that melanocytes are absent from the depigmented skin.

Finally, vitiligo patches that do not respond to medical therapies can be repigmented surgically (see Chapter 24). The successful use of autografts of various types to repigment depigmented skin indicates that the epidermis is capable of supporting a population of visible, identifiable and functioning melanocytes. There are numerous successful techniques to transplant autologous melanocytes from one site on the integument to another (Behl & Bhatia 1973; Bonafe *et al.* 1983; Suvanprakorn *et al.* 1985; Beck & Schmidt 1986; Falabella 1983, 1986, 1988; Koga 1988; Brysk *et al.* 1989; Gilhar *et al.* 1989; Plott *et al.* 1989; Chitale 1991; Gauthier & Surleve-Bazeille 1992; Zachariae 1994; Agrawal & Agrawal 1995; Boersma *et al.* 1995; Hann *et al.* 1995; Kahn & Cohen 1995). That surgical techniques repigment skin when medical therapies are unsuccessful can be interpreted to indicate that there is no factor produced by the keratinocytes that is responsible for dedifferentiating melanocytes. If the keratinocytes were masking (without killing) melanocytes, then surgical therapies should be no more successful than medical therapies. Surgical therapies are a simple but neat method to replace a missing reservoir.

The data presented in this chapter all support only one conclusion, i.e. that the white skin of vitiligo is characterized by the loss of melanocytes from the epidermis. In this monograph, this conclusion will be the basis for many comments and recommendations.

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3: History and Cultural Aspects of Vitiligo

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Historical references about vitiligo

Several authors have noted interesting ancient, historical references to vitiligo (Brocq 1892; Sutton 1965; Goldman *et al.* 1966; Nair 1978; Lee 1982; Ortonne *et al.* 1983; Koranne & Sachdeva 1988; Hann & Chung 1997). However these commentaries may be contested by historians as references to vitiligo because of semantic difficulties and possible errors in the translation and interpretation of ancient writings. Therefore, the following review has to be seen more as a chapter reviewing historical writings on 'patchy skin lesions', some of which might be vitiligo but not necessarily all.

Vitiligo in writings from dates before Christ (BC)

The earliest reports on patchy skin diseases that may be interpreted as today's vitiligo date back to approximately 1500BC. The *Ebers Papyrus* mentions two types of skin diseases characterized by changes in the colour of the skin. One disorder could be interpreted as leprosy as 'thou shalt not do anything to it'. The other seems to be characterized only by a lack of pigmentation and is likely to be vitiligo (Nair 1978).

References of the same age can also be found in the ancient vedic scripture of India, *Atharva Veda* (Koranne & Sachdeva 1988). It reports on the disease 'Kilas'. The term 'kilas' derives from the sanskrit word 'kil' meaning 'white' in the sense of 'casting away'. In a translation of the *Atharva Veda* in 1905 'kilas' was equated with the term 'vitiligo'. A collection of Shinto prayers from the Far East known as *Makatominoharai* (1200BC) report on 'shira bitu' meaning 'white man', and in some incidences it may also be interpreted as vitiligo. *Charak Samhita* (800BC), another medical compilation found in the Indian literature, mentions a disease called 'svitra', a sanskrit word meaning 'spreading whiteness'. The *Ashtangahidaya* (600BC) tries to explain prognostic factors of these eruptions (Nair 1978). For the management of white spots, in ancient Egypt or India, the active ingredient of *Psoralea corylifolia* or *Ammi majus* was applied on depigmented spots and exposed to sunlight.

Much emphasis on 'white spots' can be found in the Greek literature. Herodotus (484–425BC), a Greek historian, wrote in his book *Clio* that foreigners who suffered from such lesions, must have 'sinned against the sun'

and had to leave the country immediately (Goldman *et al.* 1966). The Indian *Manu Smirti* (200BC) describes 'Sweta Kushtha', meaning 'white disease', skin lesions which probably were vitiligo (Koranne & Sachdeva 1988).

Biblical references to vitiligo

The Bible refers to certain skin conditions using the Hebrew word 'Zara'at' in Leviticus XIII in the Old Testament. This term in actuality alludes to many different cutaneous afflictions. Some of them have been interpreted as the sign of a sin, which in Hebrew theology symbolizes a punishment sent by God. The term 'Zara'at' in the Bible denotes 'white spots' but this does not necessarily indicate vitiligo (Goldman *et al.* 1966). The roots of this controversy about the different interpretations of 'Zara'at' can be found from the events occurring around 250BC when Ptolemy II demanded the translation of the Bible into Greek in order to make it understandable to a larger population. For all statements where a human being is declared unclean by reason of 'Zara'at', the scholars of the Septuagint retained the term 'leprosy' without regard to modern dermatological terminology (Leviticus XIV, 34). The confusion arising from this definition is an important cause for the social stigma attached to 'white spots on the skin' as they may either denote leprosy or vitiligo or many other cutaneous lesions (Table 3.1). Since then theologians also proposed the term 'psoriasis' to be used synonymously for these afflictions. They reasoned that to change the biblical concept of leprosy, the substitution of the term 'psoriasis' seemed useful because it does not denote the idea of an associated 'moral sin'. The term psoriasis in the Bible should be understood to mean any 'affection of the skin'.

For many years dermatologists have been interested in the true nature of 'biblical white spots'. Most dermatologists have concluded that the medical terms used in the Bible are not related to leprosy in many instances. Rather, the terms probably represent a variety of skin conditions and sometimes also mean vitiligo (Table 3.1) (Goldman *et al.* 1966).

Table 3.1 Classification of the meaning of 'White spots' in the Bible (see also Goldman *et al.* 1966).

Description of the Lesion	Interpretation
White spots per se	Vitiligo
White spots associated with inflammation	Postinflammatory leucoderma Leprosy (?)
White spots associated with scaling	Psoriasis Leprosy (?)
White spots associated with atrophy	Morphea Leprosy (?)
White spots associated with the regrowth of hairs which turn white	Alopecia areata

Vitiligo references from writings Anno Domino (AD)

It is said that in the Chinese literature skin disorders were mentioned much earlier than in western literature but their descriptions were rather vague. Around 600AD Dohi wrote clear descriptions of 'Pin-yüan-hon-lun' which was probably today's lepra (Goldman *et al.* 1966). In ancient Arabic books 'white skin' was expressed as 'baras' and with terms like 'bahak' or 'bohak' (Koranne & Sachdeva 1988). From the Koran the story has been transmitted that Jesus was able to cure patients with 'baras' (Ortonne *et al.* 1983). Patchy skin lesions, likely to be of a leprous nature, were the most important cutaneous diseases that were mentioned in the writings of the early European medical schools up to the 15th Century. At the end of that century leucoderma syphiliticum became a new, important differential diagnosis as the number of lepers decreased and the 'new' lues venera, later known as syphilis, spread far and wide over Europe.

In Korea, hypopigmentary disorders, such as vitiligo, tinea versicolor, naevus depigmentosus, naevus anaemicus and albinism, as well as their treatment, were written about in an old Korean Oriental medical book published in the early 17th Century, the *Doney Bogam*. As a method of treatment sulphur or specially formulated arsenic or mercury ointment was applied on vitiligo lesions and primitive phototherapy was used (Hann & Chung 1997). An example of vitiligo was drawn on the portrait of Chang-Myeong Song (1689–1767), a high ranking official of the Yi dynasty of Korea (1392–1910) (Fig. 3.1) (Lee 1982). There was obviously no misconception about vitiligo in Korea. Otherwise a portrait of a member of the noble class showing vitiliginous skin would not have been published.

Fig. 3.1 Portrait of Chang-Myeong Song (1689–1767), a high ranking official of the Yi dynasty of Korea (1392–1910), showing vitiligo. (See also Lee 1982).

The origin of the word vitiligo

The word 'vitiligo' itself is said to have been first used by Celsus in his Latin medical classic *De Medicina* in the 1st Century AD. Regarding the roots of the term 'vitiligo' there seems to be some difference of opinion between lexicographers and dermatologists. Some suggest that the word vitiligo comes from the Latin word for veal because the white skin has an appearance resembling the white glistening of the flesh of calves ('vituli'). Others suggest that it may be derived from 'vitelius', the Latin word for 'calf' itself because of the white patches in a calf's fur. Some early writers, like Hieronymus Mercurialis who wrote in the 16th Century, believed that the word vitiligo represents a blemish or fault which in Latin is called 'vitium'. The addition of the 'l' in the word 'vitiligo' is uncertain. It may just have been introduced for reasons of euphony (Nair 1978; Ortonne *et al.* 1983). Finally, the *Lexicon of the Latin Language* published by Facciolati and Forcellini in Boston 1841, did not clarify the origin of the terminology. Instead of settling the confusion this lexicon aggravated the issue by its statement, 'Vitiligo (vitium): a kind of leprosy or cutaneous eruption consisting of spots, sometimes black (?), sometimes white, called morphea, alphus, melas, leuce; also in general a cutaneous eruption. Celsus & Pliny' (2nd Century AD) (Sutton 1965).

Vitiligo in the 19th Century

Near the end of the 19th Century, when skin diseases were still presented in alphabetical order in many textbooks of dermatology, vitiligo was defined as a pigmentary dystrophy. Moreover, Louis Brocq (1856–1928) noted the lack of pigmentation (achromy) in vitiliginous lesions combined with an increase of pigmentation (hyperchromy) in the lesion's periphery which he called 'dyschromy' (Brocq 1892). Moritz Kaposi (1837–1902) was one of the first to describe the histopathological features of vitiligo. He stated that the only anatomical change in vitiliginous skin is the lack of pigment granules in deep rete cells. In the periphery of the lesion there is an increase of pigmentation. Sparse pigment laden cells in the corium are unable to add much to the clinical aspect of the skin's pigmentation (Fig.3.2) (Kaposi 1879).

Obscure aetiological mechanisms like emotional stress or other traumatic factors triggering the eruption of vitiligo have been discussed by our dermatological forefathers. For them, a connection with the nervous system seemed to be evident (Neumann 1880; Brocq 1892).

At the turn of the century different approaches were made in the treatment of vitiligo. Systemic administration of bromides, iodides or valerianates, of mercury, antimony, and arsenic did not show much effect. Ernest Besnier (1831–1909) recommended subcutaneous injection of pilocarpine, and saline or bromoiodic baths. Different mixtures with croton oil, iodine, sublimate, and naphtol have been used topically without convincing therapeutic results (Neumann 1880; Brocq 1892).