Treatment of vitiligo

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CHAPTER 2

Vitiligo: A review

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"White discolorations of the skin" have been described since ancient history. Although the term "vitiligo" was introduced only in the first century AD, many investigators believe that these ancient descriptions referred to the disease presently known as vitiligo.

According to the review articles by Nair in 1978 and Srivastava in 1994 the first citations of the disease can be found in the classic book "Tarikh-e-Tibb-e-Iran", dated from the period of Aushooryan (2200 BC). Two types of diseases characterized by discolorations of the skin were described by pharonic medicine in the "Ebers Papyrus" (1550 BC), one with swellings referring to leprosy ("thou shall not do anything to it") and the other only macular and probably referring to vitiligo ("thou findest only change of color"). The latter condition was regarded to be "treatable".

Hundreds of years before Christ vitiligo was mentioned in ancient Indian sacred books. In Atharva Veda (1400 BC), the term "kilas" can be found. The Sanskrit word "kilas" is derived from Kil, meaning white as meaning to throw or to cast away. So "kilas" means that which throws away color. Also the term "shweta khusta" was used meaning, "white leprosy". "Kustha" means "obstinate skin diseases including leprosy" in Hindi language, which suggests that vitiligo was probably confused with macular leprosy. The disease was called "Safed Korh" and was thought to be caused by eating white colored food, such as milk and fish. Villagers in referring to this disease have also used the word "charak". "Charak" means "that which spreads or is secret" ("secret disease"). In the Buddhist sacred book Vinay Pitak (624-544 BC) the term "kilas" was also used to describe the white spots on the skin. Men and women with kilas were not eligible for ordainment.

Descriptions of vitiligo can also be found in other ancient Indian writings such as the Charaka Samhita (800 BC) and Manusmriti (200 BC). Patients suffering from this disease were not respected in society. In Amorkasha (600 AD), the word "Svitra" (meaning "leukoderma") was used together with "padasphota" (flower of legs), "twakpuspi" (flower of skin) and "sidhmali" (spreading whiteness).

In the Arabian literature, the names "Bohak" and "Baras" are used to describe vitiligo. "Baras" means, "white skin". In the Holy Koran (chapter 3 verse 48 and chapter 5, verse 109) we can read;

"In accord with God's will, Jesus was able to cure patients with Baras".
The early classics from the Far East, such as Makatominoharai, a collection of Shinto prayers, also mentioned the existence of a skin disease with white spots called “Shirabito” which literally means “white man”.

In the Old Testament of the Holy Bible we can find the Hebrew word “Zoráat” in Leviticus 13. Zoráat referred to a group of skin diseases that were classified into five categories; (1) white spots per se (2) white spots associated with growth of white hairs (3) white hairs associated with inflammation (sore) (4) white spots with scaling and (5) white spots with atrophy. Of these, the first two are most probably vitiligo. The others are not. It seemed that also in this period, persons with leprosy, vitiligo, post-inflammatory hypopigmentation or other leukodermas were regarded as having the same skin affection. The word Zoráat has been unfortunately translated in Greek and English versions of the Bible as “white leprosy”. This mistranslation could be an important cause for the social stigma connected to “white spots on the skin”. Consequently, persons with white spots independent of the cause were isolated from the healthy ones;

“Anyone with this skin affection must wear torn clothes and have his hair all disheveled; he must conceal his upper lip, and call out, “Unclean, unclean”. So long as the disease persists, he is to be considered ritually unclean, and live alone, staying outside the camp” (Leviticus 13: 45-46)

In ancient Greek medical writings white spots and their social implications have also been mentioned by the historian Herodotus (484-425 BC) in his book “Clio” 1, 138, written in 449 BC;

“If a Persian has leprosy or white sickness he is not allowed to enter into a city or to have dealings with other Persians, he must they say, have sinned against the sun. Foreigners attacked by this disorder are forced to leave the country even white pigeons are often driven away as guilty of the same offence”

Nowadays, patients with vitiligo are still regarded as social outcasts in certain countries (India, Pakistan).

The word “vitiligo” was probably first used in the first century AD (circa 30 AD) by the Roman physician Celsus in his Latin medical classic “De Medicina”. It is still a debate whether vitiligo was derived from the Latin word “vitium” or “vitulum” respectively
meaning “blemish” and “small blemish” or from the Latin word “vitelius” meaning “calf”, referring to the white and glistening appearance of the skin of this animal. According to Nordlund, the term could be a contraction of the Latin words “vitilenum egeo”, which translated freely means, “I wish to see the madam of this bordello”. Because leukoderma is a symptom of venereal disease, it is possible that most forms of leukoderma were regarded a single entity. Whatever the origin of the term, all these Latin words indicate a white spot on the skin.

Treatment of vitiligo in ancient times

Two drugs are mentioned in the Atharva Veda (1400 BC), namely “asikni” and “shyama” (meaning that which tans the skin) that on topical application, can produce repigmentation of the skin. These drugs were probably derived from certain herbs or plants and were praised in the hymn below;

"Born by night art thou, O plant,
Dark, black, sable, do thou,
That art rich in color, stain,
This leprosy and white gray spots.
Even color is the name of thy mother,
Even color is the name of thy father,
Thou O plant produces even color
Render this (spot) to even color”.

According to Indian medicine books the two most commonly applied and effective herbs were “Malapu” (Ficus hispida) and “Bakuchi” or “Bavachi” (Psoralea corylifolia). These herbs were administered “orally or topically followed by exposure to sunlight until sweating occurred. Blisters are then produced in the skin and after their rupture, repigmentation occurred”.

In the Charaka Samhita we can read:

“He should expose himself to sun rays according to his capacity”

Both these herbs are now known to contain psoralens.

The Egyptians made use of the dried fruit of the plant “Ammi Majus” that grows
freely in the Nile Valley. The first reference to the use of Ammi Majus is found in the Arabic book “Mofradat El-Adwiya” written by Ibn El Baitar, who lived in the 13th century AD. Egyptian herbalists used these herbs in the form of a powder that they named “Aatrillar”

The prognosis of vitiligo has also been described in detail in ancient books. Vagbhata wrote in “Ashtanga Hridaya” (600 AD), which is a compilation of ancient Indian medicine the following.

“Switra (=vitiligo) can be cured,
1. If the hair over these patches has not turned white
2. If the patches are not numerous
3. If the patches are not connected with each other
4. If the patches have freshly occurred, and
5. If the patches are not caused by burns”

Another condition termed as “kilá sa”, referring to a more serious type of leukoderma than svitra (unclear whether this was also vitiligo) was regarded as being “incurable if the patches were present in the genital and anal regions, palms and lips, even if these patches were fresh. Such patients should never be treated if the physician desired to be successful in life”

Several other ancient masters of medicine pertinently made these observations. In his classical work “Prognostic” Hippocrates also observed that “these complaints (=vitiligo) are the more easily cured the more recent they are, and the younger the patients, and the more the soft and fleshy the parts of the body in which they occur”. Remarkably, the prognoses of ancient physicians regarding the response of vitiligo to therapy are nowadays still applicable for most forms of repigmentation therapy.

2.2 EPIDEMIOLOGY

Prevalence and incidence of vitiligo

The prevalence of vitiligo in the population is often estimated to be about 1% 17. When reviewing the literature, it appears that most estimates are based on biased samples (e.g., hospital patients, patients with autoimmune disorders, retrospective samples of case notes in hospitals). Such estimates are often misleading and should not be extrapolated
to the general population without correction. Moreover, in some studies, the term "prevalence" was used while, from the epidemiological point of view, the term "incidence" would have been more appropriate. In addition, varying social, cultural, and environmental factors can influence patients' decision whether or not to consult a doctor for their skin disease. Apparently, higher incidence rates of the disease are reported in populations where the color contrast is more obvious and where still some stigma is connected to the white spots. As a result, different studies in different regions report different incidence rates, as shown in Table 1.

Only a few population surveys have been performed. Mehta et al. in 1973 performed an extensive study in India around the city of Surat by investigating households and examining family members; the prevalence of vitiligo was 0.47% in 1.887 rural inhabitants and 1.78% in 7.178 urban citizens. Prevalence data for vitiligo in the general population of the United States of America (USA) were collected more than 20 years ago as part of the first National Health and Nutrition Examination Survey (NHANES). In this survey, more than 20.000 subjects between 1 to 74 years old were included; results indicated that the prevalence of vitiligo in the USA was 0.5%. In 1979, Howitz et al. surveyed 47.033 individuals living in the Isle of Bornholm, Denmark, for the presence of vitiligo; they observed a prevalence of 0.38%. In a more recent study, 15.685 individuals in Calcutta were screened; the authors reported a prevalence of vitiligo of 0.5%. From these data, we may conclude that the prevalence of vitiligo in the general population is closer to 0.5% rather than to 1%.

Racial distribution

Although there is a clinical impression that vitiligo occurs more frequently among dark-skinned individuals, it is generally believed that the disorder equally affects individuals of all ethnic origins.

Sex

Vitiligo shows no special predilection for either sex. In general, more women than men seek medical advice probably because they are cosmetically more aware of their pigmentary disorder. In the clinic, the ratio female: male with vitiligo is usually 2-3:1. On the contrary, other studies have found that there were more male than there were female patients with vitiligo. Some epidemiological studies showed that among the studied population of children with vitiligo, there were more girls than there were boys.
This can be attributed to the fact that parents are probably more concerned when confronted with a daughter instead of a son with vitiligo and therefore are more likely to consult a doctor.

Table 1. Reported incidence rates of vitiligo based on clinical records. A summary of the literature

<table>
<thead>
<tr>
<th>First author and year of publication</th>
<th>City / Country</th>
<th>Patient population *</th>
<th>Incidence in %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panjoo, 1947 18</td>
<td>Calcutta, India</td>
<td>DC</td>
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</tr>
<tr>
<td>Banerjee, 1956 19</td>
<td>Calcutta, India</td>
<td>DC</td>
<td>2.5</td>
</tr>
<tr>
<td>Levoi, 1958 20</td>
<td>Vellore, India</td>
<td>DC</td>
<td>4.0</td>
</tr>
<tr>
<td>Lahiri, 1959 21</td>
<td>Calcutta, India</td>
<td>DC</td>
<td>6.0</td>
</tr>
<tr>
<td>Punshi, 1969 22</td>
<td>Amravati, India</td>
<td>DC</td>
<td>8.0</td>
</tr>
<tr>
<td>Dutta, 1969 23</td>
<td>Calcutta, India</td>
<td>DC</td>
<td>4.3</td>
</tr>
<tr>
<td>Behl, 1972 24</td>
<td>Delhi, India</td>
<td>DC</td>
<td>8.8</td>
</tr>
<tr>
<td>Sahgal, 1974 25</td>
<td>Ggo, India</td>
<td>DC</td>
<td>2.9</td>
</tr>
<tr>
<td>Karanne, 1988 26</td>
<td>Delhi, India</td>
<td>DC</td>
<td>1.25</td>
</tr>
<tr>
<td>Jaisankar, 1992 27</td>
<td>Pondicherry, India</td>
<td>DC</td>
<td>2.6</td>
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<tr>
<td>Arokawa, 1938 28</td>
<td>Japan</td>
<td>DC</td>
<td>1.64</td>
</tr>
<tr>
<td>Itie, 1952 29</td>
<td>Sendai, Japan</td>
<td>DC</td>
<td>1.3</td>
</tr>
<tr>
<td>Khoo Oon Teik, 1962 30</td>
<td>Singapore</td>
<td>GH</td>
<td>0.7</td>
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**EUROPE**

<table>
<thead>
<tr>
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<th>City / Country</th>
<th>Patient population *</th>
<th>Incidence in %</th>
</tr>
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<tr>
<td>Polotebnoff, 1922 31</td>
<td>Russia</td>
<td>DC</td>
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<tr>
<td>Fornare, 1925 32</td>
<td>Italy</td>
<td>DC</td>
<td>0.3</td>
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<tr>
<td>Robert, 1943 33</td>
<td>Switzerland</td>
<td>DC</td>
<td>0.39</td>
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<tr>
<td>Dowber, 1968 34</td>
<td>England</td>
<td>GH</td>
<td>0.67</td>
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<td>Grunnet, 1970 35</td>
<td>Denmark</td>
<td>GH</td>
<td>1.44</td>
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<td>Perrot, 1973 36</td>
<td>France</td>
<td>DC</td>
<td>0.6</td>
</tr>
<tr>
<td>Desmons, 1974 37</td>
<td>France</td>
<td>DC</td>
<td>3.0</td>
</tr>
<tr>
<td>Siragusa, 1999 38</td>
<td>Troina, Italy</td>
<td>GH</td>
<td>1.2</td>
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</table>

**NORTH AND SOUTH AMERICA**

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<th>Incidence in %</th>
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<tr>
<td>Canizares, 1960 39</td>
<td>Mexico</td>
<td>DC</td>
<td>2.9 ; 3.4; 4.3; 5.3; 6.7 †</td>
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<tr>
<td>Fitzpatrick, 1974 41</td>
<td>Massachusetts, USA</td>
<td>DC</td>
<td>8.0</td>
</tr>
<tr>
<td>Ruiz Maldonado, 1977 44</td>
<td>Mexico</td>
<td>DC</td>
<td>2.6</td>
</tr>
</tbody>
</table>

* DC indicates dermatological outpatient clinic; GH, general hospital
† measured at 5 different time periods in 3 different hospitals
Age

Vitiligo may occur at any age. However, the disease is seen most frequently among young people. A Dutch epidemiological study that involved 1061 patients with vitiligo showed that 25% of the patients noted the onset of vitiligo before the age of 10 years, 50% before 20 years and 95% before the age of 40. Of the total population of patients with vitiligo, between 23% and 26% are reported to be children younger than 12 years. There are also reports on "congenital vitiligo". However, the depigmentation that was observed at birth could be mistaken for the congenital pigmented disorder piebaldism. Because the neonatal skin was not yet exposed to natural sunlight, it is possible that the hyperpigmented spots within the white lesions, which are typical hallmarks of piebaldism, were not yet visible.

2.3 GENETICS

A positive family history for vitiligo has been reported to be present between 6.25% to 38% of the cases according to several independent studies. Vitiligo has also been described in monozygotic twins. There are several theories regarding the mode of inheritance of the disease. An autosomal dominant pattern of inheritance with variable expression and penetration has been postulated. A theory describing the involvement of recessive alleles at a set of four unlinked diallelic loci has also been put forward by some authors. However, in most studies where an aggregation of vitiligo within kinships has been shown, only one affected member has been reported, occasionally two. These observations suggest that vitiligo may not be transmitted in a simple Mendelian autosomal dominant or recessive manner. The transmission is therefore thought to be complex and polygenic with variable expression of the genes involved. In 131 Japanese patients with nonsegmental vitiligo, Ando et al. found that familial patients developed vitiligo lesions at a significantly earlier age than nonfamilial patients.

Studies performed in different countries on the relationship between the Human Leukocyte Antigen (HLA) system and vitiligo showed variable findings. Gunter and Richter in 1975 found an increased prevalence of HLA-B13 in 28 German patients. Retornaz et al. in 1976 could not confirm any correlation of HLA and vitiligo in a study among French patients. However, they found that HLA-B13 was more prevalent among
patients with vitiligo with antibodies against thyroid gland antigens. Foley and colleagues in 1983, found an increased prevalence of HLA-DR4 alleles in 48 white American patients with vitiligo\textsuperscript{74}. Among Moroccan Jews with vitiligo, a high prevalence of HLA-B13 was observed in a study performed by Metzker et al. in 1980\textsuperscript{75}. In the Netherlands, an increased prevalence of HLA-A2, HLA-DRW6, HLA-DRW52 and HLA-DQW1 has been observed\textsuperscript{76}. A significant increase of HLA-A30, CW-6, DQW-3 and a decrease of C4AQ0 have been reported in 93 patients from Northern Italy by Orecchia et al. in 1992\textsuperscript{77}. Also Lorini et al. who examined 88 patients from Italy, showed a positive correlation between HLA antigens, the presence of autoantibodies and heavy chain (Gm) and light chain (Km) allotypes\textsuperscript{78}. A study completed in Hamburg on 102 patients compared with 400 unrelated age and sex matched controls showed that the rare antigen DRW-12 and HLA-A2 were significantly increased\textsuperscript{79}. Ando et al. found in 131 Japanese patients that there was a significant association between HLA-B46 and familial nonsegmental vitiligo, whereas HLA-A31 and CW4 were found in nonfamilial patients\textsuperscript{70}.

Other more recent studies indicated that mutations in certain genes could be associated with the pathogenesis of vitiligo. De la Fuente-Fernandez et al. in 1997 found mutations in the gene encoding for GTP-cyclohydrolase I (GTP-CH I), which is the rate limiting enzyme in tetrahydrobiopterin synthesis. A decrease of GTP-CH I may lead to a diminished supply of tyrosine from phenylalanine\textsuperscript{80}. Another study found an increased prevalence of patients with vitiligo (11%) among patients with the mitochondrial encephalomyopathy lactic acidosis and stroke like episode syndrome (MELAS). Among the patients with vitiligo, bp 3243 mutation in mitochondrial DNA could be detected. The investigators proposed that this mutation in vitiligo may lead to dysfuncitoning but not to complete disappearing of melanocytes in the epidermis\textsuperscript{81}. So far, all these findings have not been confirmed yet.

In conclusion, genetical factors probably play a key role in the pathogenesis of vitiligo. The exact genetic defects remain to be identified.

### 2.4 CLINICAL MANIFESTATIONS

The initial symptom of vitiligo is mostly a well-defined depigmented chalk white macula that may not be noticed by the patient. Lesions can be present on any site of the body, but are usually seen on sites of stretch and pressure e.g., knees, elbows, dorsum of hands
and fingers. In the most common type, “vitiligo vulgaris” there is a remarkable symmetrical distribution of the lesions. Segmental variants of vitiligo are rare.

The margins of the lesions are often hyperpigmented. Sometimes hypopigmented lesions occur together with the depigmented spots in the same patient. This type is called “trichrome vitiligo”, because three colors, brown (unaffected skin), tan (light brown) and white can be seen. “Quadrichrome vitiligo” refers to another variant of vitiligo showing the presence of a fourth color, dark brown at sites of perifollicular repigmentation. The term “pentachrome vitiligo” was introduced by Fargnoli in 1995, referring to a case of a black patient with vitiligo having five colors on the skin, white, tan (hypopigmentation), medium brown (unaffected skin), dark brown and black. Biopsy specimens of the depigmented areas showed a complete absence of melanocytes whereas in the hyperpigmented areas an increase of epidermal melanin could be observed. Within one year, the patient was completely depigmented. The different grades of hyperpigmentation probably reflected transitional stages of the depigmenting process.

Rarely, patients present one or several lesions with an inflammatory border where the margin of the achromatic spot shows a thin, raised, edematous and erythematous seam. This phenomenon is termed “inflammatory vitiligo” and may occur more often than observed in the clinic. Patients with inflamed vitiliginous lesions are often suspected to have an active disease, however, this has not been confirmed in a properly conducted prospective study yet. Localized whitening of scalp hair, eyebrows or eyelashes (i.e. poliosis circumscripta) can be frequently observed. Canities or premature graying can be closely related to vitiligo also. The majority of patients with vitiligo experience increased sensitivity to sun exposure of their depigmented skin, whereas the uninvolved skin tans without any difficulties.

The natural course of the disease is usually unpredictable, but is often progressive. After years of stabilization, a sudden exacerbation may occur. A more rapid progressive form of vitiligo may lead to a complete depigmentation of the whole integument within 6 to 12 months after onset of the disease. Spontaneous repigmentation has been reported to occur in 6% to 44% of the patients. Cases of previously totally depigmented individuals who spontaneously regain most of their original color have been reported, but are very rare. When spontaneous repigmentation does occur, it is usually noted in only one or a few maculae and occurs perifollicular or from the margins of the lesion. A perifollicular pattern of repigmentation strongly suggests that melanocyte reserves are located in the hair follicles and also along the outer sheets of the hair shafts. In the face,
a more diffuse pattern of repigmentation may be observed. Spontaneous repigmentation is usually also a sign that the patient will respond well to therapy.

2.5 CLASSIFICATION

Several classification systems have been proposed in literature. Most of them are based on the distribution or localization of the depigmented lesions (Figure 1). Ortonne in 1983, suggested the classification as presented in Table 2. Koga and Tango in 1988 suggested type A (nondermatomal, generalized) and type B (dermatomal, segmental, and localized). Type A was regarded an autoimmune disease that responded well to corticosteroid therapy. Sympathetic dysfunction might play a causative role in type B that did not respond to corticosteroids, though was treatable with oral nialamide.

![Classification of vitiligo](image)

Figure 1. Classification of vitiligo. (A) Vitiligo focalis, (B) Vitiligo segmentalis, (C) Vitiligo acrofacialis, (D) Vitiligo vulgaris, (E) Vitiligo universalis.
Table 2: Classification of vitiligo (according to Ortonne, 1983)

<table>
<thead>
<tr>
<th>Localized vitiligo</th>
<th>Generalized vitiligo</th>
<th>Universal vitiligo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. <strong>Focalis</strong>: only one or more macules in one area, not clearly in a segmental or zosteriform distribution</td>
<td><strong>Acrofacial</strong>: distal extremities and face</td>
<td><strong>Universalis</strong>: &gt;80% depigmentation</td>
</tr>
<tr>
<td>2. <strong>Segmentalis</strong>: one or more macules in a quasi-dermatomal pattern</td>
<td><strong>Vulgaris</strong>: scattered macules over the entire body with a symmetrical distribution pattern</td>
<td></td>
</tr>
<tr>
<td>3. <strong>Mucosalis</strong>: only mucous membrane(s) affected</td>
<td><strong>Mixed acrofacialis and/or vulgaris and/or segmentalis</strong></td>
<td></td>
</tr>
</tbody>
</table>

2.6 PSYCHOSOCIAL ASPECTS

Studies in the United States revealed that vitiligo may cause serious psychosocial problems for those afflicted. Patients are painfully aware of their unattractive appearance caused by white spots usually present on the face, neck, and hands or even by those on covered parts of the body such as the genitalia. Most patients reported to have a low self-esteem and to experience a high degree of anxiety and embarrassment particularly when they meet strangers or begin new personal relationships. Many experienced unpleasant staring by others and believed that they had been victims of rude remarks. Some are sexually inhibited, whether married or not. Those who have or desire a job requiring frequent contact with the public have lost jobs or have been rejected from jobs. The increased sensitivity to sun exposure in the lesions may lead especially during summertime, to limitations of the recreational and social lives of the patients. Data from the Dutch study showed that about one third of the patients apply excessive amounts of cosmetics or wear special clothes to cover their lesions, such as gloves, long sleeves, turtlenecks or sweaters, even during the hottest days of summer. The quality of life of at least one third of the patients is significantly impaired by the disease. For those people especially living in the tropics vitiligo carries additional cultural burdens and social penalties, because of its resemblance with leprosy.

Many patients feel distressed by the attitude of many physicians towards the disorder. They were told that vitiligo was merely a “cosmetic disorder “ and that they “should just have to learn to live with it”. Physicians were not perceived by the patients to be emotionally
supportive or sympathetic to their skin disorder and its impact on their lives. Sufferers have experienced disinterest and lack of concern from their doctors. The failure of many physicians to give vitiligo the status of a “bona fide” disorder that deserves as much care and attention as other (chronic) skin disorders such as psoriasis and atopic dermatitis, is also reflected by the attitude of most health insurance companies. They avoid payment for treatment of vitiligo, because any treatment for vitiligo is classified as a “cosmetic or plastic surgical correction”. Within this social and cultural environment, it is not surprising that many patients become discouraged to seek therapy.

The psychosocial impact of vitiligo on children may also not be underestimated. The study in the Netherlands demonstrated that 31% of the children with vitiligo were frequently taunted by their classmates because of having the disease. However, no control group was included in this analysis. Educating both the teachers as well as the students can solve many of the misjudgments around the disease. Children in late grade or high school can be encouraged to present a lecture or science project on vitiligo and the pigmentary system to help their classmates to better understand the nature of the disease.

2.7 ASSOCIATED DISORDERS

There are some cutaneous and internal disorders that are reported to occur more frequently among patients with vitiligo.

Autoimmune disorders

It has been frequently observed that certain autoimmune disorders are associated with vitiligo. These include multiple glandular insufficiencies, thyroid disorders (hypothyroidism, hyperthyroidism or thyroiditis), pernicious anemia, juvenile diabetes mellitus, Addison’s disease, and autoimmune hyperparathyroidism. In addition, several circulating antiorgan antibodies can be demonstrated among patients with vitiligo. The hypothesis that vitiligo may also be an autoimmune disorder was based upon these clinical findings. Surprisingly, a more recent study on 321 German patients with vitiligo strengthened significant association only with thyroid disorders, whereas none of the other disorders previously linked to vitiligo could be confirmed.
CHAPTER 2

Ocular and auditory and meningeal involvement

Because melanocytes are not only found in the skin and mucosa, but also in the leptomeninges, uveal tract and retinal pigment epithelium of the eye and the stria vascularis of the inner ear, some investigators have studied the occurrence of abnormalities of these organs in relation to vitiligo.

Ocular abnormalities have been reported among patients with vitiligo. These include uveitis, retinal pigment epithelium hypopigmentation and depigmentation, chorioretinal scars, pigment clumping, retinitis pigmentosa, iris transillumination defects and heterochromia irides. Conversely, a prevalence of vitiligo varying between 1.5% to 5% has been found among patients with idiopathic uveitis.

The Vogt-Koyanagi-Harada syndrome is a rare multisystem disorder, characterized by an acute severe uveitis, meningo-encephalitis and deafness, followed by the appearance of poliosis, alopecia areata and vitiligo. The consulting dermatologist will often encounter the syndrome in a later disease stage. It is however, essential to recognize the disorder in an early phase because ocular complications, including blindness, may be prevented by immunosuppressive therapy. Another rare primary ophthalmologic disorder associated with vitiligo is the syndrome of Alezzandrini. Patients with this syndrome, usually young of age, show an unilateral tapetoretinal degeneration, followed by ipsilateral vitiligo and poliosis of the face. Sometimes perceptual deafness may occur.

Studies on the occurrence of (inner) ear abnormalities among patients with vitiligo reveal contradictory results. Tosti et al. in 1987 found the prevalence of auditory problems among patients with vitiligo to be higher than in control patients without vitiligo (16% in 50 patients compared with 0% in 40 controls). These abnormalities included minimal audiometric changes or moderate hypacusis, either unilateral or bilateral. However, this study does not provide evidence that the defects were present in the melanocytes. Two other studies by Orechia et al. in 1989 and by Escalante-Ugalda et al. in 1991 revealed that the prevalence of audiologic disturbances was not increased among patients with vitiligo.

No hearing or ocular abnormalities were diagnosed in 321 patients with vitiligo in the Hamburg study. These findings are surprising since the oldest patient with vitiligo that was included in the study was 85 years old.

Dermatological disorders

Some common dermatoses such as psoriasis vulgaris, scleroderma, lupus erythematosus, alopecia areata and M. Duhring have also been frequently observed in association with vitiligo. Most of these reports are however, case reports...
and the data should be confirmed in a larger study that includes a control group.

**Melanoma and vitiligo**

"Vitiligo-like depigmentations" have also been frequently observed among patients with melanoma. Many authors believe that this symptom may improve the prognosis of vitiligo \(^{111-114}\). It is still a point of discussion whether the mentioned depigmentations or "melanoma associated leukoderma" should be regarded as identical to vitiligo \(^{115}\).

Also, there is still debate whether patients with vitiligo are more prone to develop melanoma. In a case-control study including 623 patients with melanoma in Northwestern Europe, Schallreuter et al. found that there was a 7 to 10 fold increase in the prevalence of vitiligo in patients with melanoma compared with the prevalence of vitiligo in the general population i.e. about 0.5%. A reverse analysis of the data showed a 180-fold higher prevalence of melanoma among patients with vitiligo \(^{116}\). In contrast, Lindelof et al., found only 3 cases of melanoma among a population of 1052 patients with vitiligo (prevalence of 0.3%). Two of them had developed vitiligo after melanoma was diagnosed and only 1 developed melanoma 32 years after the diagnosis of vitiligo\(^ {117}\). From the latter study, it seems that is not necessary to perform a more than normal examination of patients with vitiligo for the presence of primary melanoma.

The association of vitiligo with other disorders suggests that vitiligo could be a systemic rather than merely a dermatological disorder. However, the findings of the studies as described above should be viewed carefully. Studies have reported inconsistent findings and most studies were case reports. Furthermore, most studies did not mention whether the control group was age-matched. Because in most patients with vitiligo, the general health is unaffected, a routine screening for the presence of autoimmune disorders, neurological, ocular or auditory abnormalities is not warranted in daily clinical practice.

### 2.8 PRECIPITATING FACTORS

Although the cause for vitiligo is unknown, certain factors have been identified to play an important role in the initiation and the progression of the depigmenting process \(^{57, 118, 119}\). A questionnaire among 1061 Dutch patients with vitiligo revealed that most patients were able to recall one or more precipitating factors of their skin disorder \(^{50}\). These factors can be divided into endogenous and exogenous factors (see Table 3).
CHAPTER 2

1. Endogenous factors

In 22% of the cases a physical “stressful” event was indicated as luxating factor (puberty, pregnancy, menopause, febrile disease). Remarkably, most of these events are hormonally regulated.

Table 3. Precipitating factors for vitiligo

<table>
<thead>
<tr>
<th>I. Endogenous factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>- genetic factors</td>
</tr>
<tr>
<td>- physical and emotional stressful events</td>
</tr>
<tr>
<td>- associated internal disorders</td>
</tr>
<tr>
<td>- associated skin disorders</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>II. Exogenous factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>- chemicals</td>
</tr>
<tr>
<td>- drugs</td>
</tr>
<tr>
<td>- physical stimuli (Koechner phenomenon)</td>
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</tbody>
</table>

In 12% of the cases, the development of vitiligo was attributed to severe emotional stress, such as death of a beloved one, loss of job, divorce and in case of children problems at school or movement to a new school or town. It is known that emotional stress may cause other disorders, such as headaches or hypertension. The strong association between stress and the onset and exacerbation of certain skin conditions has also been recognized. A more recent study showed that patients with vitiligo endure a significantly higher number of stressful life events than do controls, suggesting that psychological distress may have contributed to the onset of their pigmented disorder. The mechanism by which emotional stress leads to the destruction of melanocytes is not yet properly investigated. A relationship between certain personality disorders and the development of vitiligo has not been demonstrated so far.

Familial vitiligo was reported in 38% of the patients, which is in close agreement with several other epidemiological studies in vitiligo.

Of the several associated autoimmune disorders, thyroid disorders, pernicious anemia, and juvenile diabetes mellitus were found more frequently among the patient population when compared with their respective prevalence rates in the general Dutch population. However, there was no control group included in this analysis, so, definite conclusions could not be drawn regarding the strength of these associations.

In 14% of the cases, vitiligo was mentioned to begin around a pigmented mole; this phenomenon, known as halo nevus, was most frequently observed in children. Halo nevi
are common among young children and teenagers. Yet, it is still unknown whether or not halo nevus should be regarded as a true risk factor in vitiligo\textsuperscript{17}. A long-term prospective study to investigate the relation between halo nevus and vitiligo is therefore warranted.

II. Exogenous factors

In 40\% of the patients the onset of their vitiligo was reported in a former scar or after a physical trauma (scratching, bumping, stubbing, grazes, burn). This is called “the isomorphic or the Koebner phenomenon”. Also the progression of depigmented lesions after sunburn can be attributed to this phenomenon. This was mentioned by 49\% of the patients. The mechanism of the Koebner phenomenon is unknown.

During the onset of the vitiligo, 16\% of the patients used certain drugs (such as beta-adrenergic blocking agents) and 19\% was exposed to certain chemicals that are reported to have melanocytotoxic properties\textsuperscript{17}. These chemicals were identified in the Dutch study as film developers (7.6\%), rubber (5.6\%), quinones (2.9\%) and bleaching agents (2.7\%).

Knowledge of precipitating factors in vitiligo may help in understanding the nature of the disease in the individual patient with vitiligo. However, it is difficult to assess whether preventing further exposure to these risk factors will also help prevent the development of new lesions or the progression of existing lesions, as suggested by Gauthier\textsuperscript{124}. Moreover, many patients are not able to indicate a luxating factor for their disorder.

2.9 HISTOLOGY

The characteristic histologic picture of a vitiligo lesion is a total absence of melanin and a total absence of identifiable melanocytes. Melanin can be visualized using the Fontana-Masson or DOPA staining methods\textsuperscript{84}. It is most likely that melanocytes are absent, though this has been a matter of discussion for a long time. Using a panel of 17 monoclonal antibodies against melanocyte specific antigens on frozen skin sections taken from vitiligo lesions, Le Poole et al. in 1993 could not observe any positive staining in the tissues\textsuperscript{25}.

In the margins of an achromic macula, aberrant melanocytes with cytoplasmic vacuolization, melanosome complexes and pyknotic nuclei may be observed by electron microscopy. In the same area, around the dermoepidermal junction, a mononuclear cell infiltrate may also be present\textsuperscript{126,127}. 
Abnormalities have also been found in keratinocytes of vitiliginous lesions. Moellmann et al. in 1982 showed the presence of cytoplasmic vacuolization and an extracellular granular material that may be originated from the cytoplasm of altered keratinocytes, mainly in the adjacent normal appearing skin, but also in the perilesional skin and rarely in the lesional skin. Bhawan and Bhutani in 1983, observed keratinocytes, especially in the basal layers of the epidermis, with intracellular vacuolization, edema and swollen cell organelles. Furthermore these investigators found colloid-amyloid depositions indicating degenerative changes. Immunohistologic studies of vitiliginous skin seem to support the above ultrastructural findings. Using different monoclonal antibodies Abdel Naser et al. (1991) detected a lack of expression of epidermal cytokeratins, a lack of expression of a basal cell marker at the margin of the lesion and a focal missing of the basement membrane antigen nicein. Moellmann and co-workers have proposed in 1982 that keratinocytes in vitiligo lesions may be altered by exposure to toxic metabolites of melanogenesis, which destroy not only the melanocyte itself, but also the keratinocyte in the neighborhood.

Degenerative changes have also been observed in sweat glands and in peripheral nerve endings of lesional skin areas. Medrano and Nordlund in 1990 showed by ultrastructural studies the presence of certain intrinsic defects (e.g. dilatations) in the structure and function of the rough endoplasmic reticulum in vitiligo melanocytes. Boissy and co-workers confirmed this finding in 1991, and they proposed that these defects may elicit a specific (auto) immune reaction leading to the death of melanocytes. However, hard evidence is still missing and so the latter remains speculative.

The situation concerning the number and functional activity of epidermal Langerhans’ cells in vitiligo is still a matter of discussion. According to some investigators, Langerhans’ cells were depleted in active vitiligo, but repopulated in stable vitiligo. Hatchome et al. reported that Langerhans’ cells were not only decreased in number but also show functional impairments.

### 2.10 Differential Diagnosis

In most cases, the diagnosis of vitiligo can be easily made from data obtained by history taking and dermatological examination. The histologic criterion of vitiligo is lack of identifiable melanocytes within the lesions. Presently, there are no valid routine
## Table 4: Differential diagnosis of vitiligo: Clinical features and Histology

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Clinical features</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piebaldism (congenital)</td>
<td>depigmentations with hyperpigmented spots, white forelock</td>
<td>absence of melanocytes, autophagocytosis within melanocytes, aberrant melanosomes</td>
</tr>
<tr>
<td>Van Waardenburg syndrome (congenital)</td>
<td>depigmentations with hyperpigmented spots, white forelock, heterochromia irides pseudohypertelorism, congenital deafness</td>
<td>absence of melanocytes, autophagocytosis within melanocytes, aberrant melanosomes</td>
</tr>
<tr>
<td>Nevus depigmentosus</td>
<td>hypopigmentation</td>
<td>decreased number of melanocytes, autophagocytosis within melanocytes</td>
</tr>
<tr>
<td>Nevus anemicus</td>
<td>hypopigmentation caused by vascular anomaly</td>
<td>no abnormalities</td>
</tr>
<tr>
<td>Tuberous sclerosis (congenital)</td>
<td>ash leaf like depigmented macules angiofibromas, epilepsy, mental retardation</td>
<td>normal number of melanocytes, small and immature melanosomes</td>
</tr>
<tr>
<td>Incontinentia pigmenti achromians (congenital)</td>
<td>hypopigmentations along the lines of Blaschko, musculoskeletal abnormalities</td>
<td>decreased number of melanocytes, immature melanosomes</td>
</tr>
<tr>
<td>Postinflammatory hypopigmentation (eczema, mycosis fungoides, psoriasis)</td>
<td>hypopigmentations at the sites of primary lesions</td>
<td>normal number of melanocytes, block in melanosome transfer (reversible)</td>
</tr>
<tr>
<td>Postinfectious leukodermia (leprosy, lues II, pinta, yaws)</td>
<td>hypopigmentations (as rest of typical signs)</td>
<td>normal number of melanocytes, block in melanosome transfer (reversible)</td>
</tr>
<tr>
<td>Pityriasis versicolor (Pityrosporon ovale infection)</td>
<td>scaling, hypopigmented macules</td>
<td>normal number of melanocytes, block in melanosome transfer (reversible), small and immature melanosomes</td>
</tr>
<tr>
<td>Pityriasis alba</td>
<td>ill-defined hypopigmentations, mainly on the face</td>
<td>normal to decreased number of melanocytes, block in melanosome transfer</td>
</tr>
<tr>
<td>Chemical/ medicamental/ physical induced leukodermia</td>
<td>hypo-/depigmentations</td>
<td>decreased number to absence of melanocytes</td>
</tr>
<tr>
<td>Idiopathic guttate hypomelanosis</td>
<td>guttate hypopigmentations</td>
<td>decreased number of melanocytes, signs of degradation of melanocytes</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>hypopigmentations, atrophy</td>
<td>decreased number of melanocytes</td>
</tr>
</tbody>
</table>
diagnostic laboratory markers available to help the clinician in making the diagnosis, in establishing the severity of the disease or in monitoring the response to therapy.

Several conditions with hypopigmentation may simulate the clinical manifestations of vitiligo (Table 4). Vitiligo is a progressive skin disorder that is difficult to treat. Some leukodermas with clinical similarity to vitiligo are reversible, have a stable course and/or are treated differently. Other forms of leukoderma can also represent a symptom for an inheritable internal or neurological disease. For these reasons, it is essential to differentiate vitiligo from these other diagnoses.

2.11 PATHOGENESIS

Several theories have been put forward to explain the pathogenesis of vitiligo. None of these theories can completely explain all the clinical and experimental observations made in this disorder. The most prevailing theories are:

1. Autoimmune hypothesis
2. Neural hypothesis
3. Self-destruction hypothesis
4. Combination of 1, 2 and 3

1. Autoimmune hypothesis

The autoimmune theory proposes that certain modifications of the immune system result in destruction of melanocytes. This defect may arise as a primary autoimmunization with formation of autoantibodies and/or autocytotoxic T-lymphocytes against antigenic determinants of the pigmentary system or the primary event may be an injury to melanocyte with release of antigenic substance and subsequent autoimmunization. The autoimmune theory is considered by many as the most attractive theory.\textsuperscript{[115]}

The immune hypothesis is initially supported by the frequent observation that several autoimmune disorders (thyroid disorders, juvenile diabetes mellitus, and Addison’s disease, pernicious anemia) are associated with vitiligo. In addition, various circulating antiorgan antibodies can be demonstrated in certain percentages of patients with vitiligo; against thyroid cells (10%), against microsomes (17%), against gastric parietal cells (13%), against adrenal cortex (2%) and against smooth muscle (5%). Also autoantibodies against mitochondria (5%) and against nuclear antigens (7%) can be found. However, other
studies have demonstrated that patients with or without associated autoimmune disorders or organ-specific autoantibodies show no significant differences regarding disease activity, severity of depigmentation or response to therapy.\textsuperscript{141,142}

Autoantibodies have also been found against certain surface antigens of melanocytes\textsuperscript{143-146}. The titers of these antibodies were shown to correlate well with the extent of depigmentation and the disease activity\textsuperscript{146,147}. Some studies have demonstrated the presence of antibodies in the sera of patients with vitiligo that were directed against tyrosinase\textsuperscript{148-153} and tyrosinase related proteins 1 and 2 (TRP-1 and TRP-2)\textsuperscript{153-156}, enzymes that play a major role in melanogenesis. In contrast, a more recent study showed that vitiligo antibodies were not directed to tyrosinase\textsuperscript{157}. So, the situation concerning the role of antityrosinase antibodies in the pathogenesis of vitiligo is still controversial. The differences as found in the various reports may be explained by differences in the detection method used and in the selection of patients, with regard to disease activity.

In the margins of lesional and normal pigmented skin of patients with active vitiligo or inflammatory vitiligo, a mild mononuclear cell infiltrate can be observed\textsuperscript{127,131,159-161}. Immunohistochemical studies indicated that T cells that are abundant in these infiltrates; T-cells may therefore play a major role in the destruction of melanocytes\textsuperscript{160-162}. Another study has shown the presence of melanocyte-specific cytotoxic T lymphocytes in patients with vitiligo\textsuperscript{163}.

Various abnormalities have also been described in peripheral blood mononuclear cells, in particular T-cells and T-cell subsets\textsuperscript{164-172}, indicating activation of these cells. However, the results of the different studies are not consistent. CD4 and CD8 positive cells and natural killer (NK) cells have been reported to be normal, decreased or increased. The variable results may arise from differences in the techniques used to determine T-cell subpopulations, as well as from differences in the patients with vitiligo studied (i.e. clinical types and disease activity). The relevance of these findings with regards to the utility as an immunologic marker is still uncertain. Many different factors are known to influence these parameters and they are obviously not standardized in any of the studies performed.

Other studies showed that the serum level of soluble IL-2 receptor (sIL-2R) was related to the disease activity in vitiligo\textsuperscript{173-175}. Increase of sIL-2R level is a sign of T-cell activation. The authors proposed that the measurement of sIL-R could be valuable in estimating the severity and the prognosis of the disease. However, one should keep in mind, that elevation of sIL-2R serum level is not a specific marker for disease activity in vitiligo as it has also been found to be correlated with disease activity of other dermatoses, such as psoriasis and atopic dermatitis\textsuperscript{176,177}.
2. Neural hypothesis

The neural hypothesis suggests the presence of a certain neurochemical mediator that is cytotoxic to pigment cells and that is secreted from nearby nerve endings. This theory is supported by the following clinical observations:

a. The occurrence of a localized form of vitiligo that seems to be confined to one segment of the body. This “segmental” variant of vitiligo is almost never dermatomal but usually affects portions of multiple dermatomes. It is also suggested that segmental vitiligo does not respond to classical vitiligo therapies, such as psoralens plus UV-A and corticosteroids, but to agents that modulate neural function.

b. The onset of vitiligo reported after a period of (severe) emotional stress. However, the mechanism how stress leads to depigmentation is unclear.

c. Vitiligo occurring in neurologically comprised skin, in a child with viral encephalitis, in multiple sclerosis with Horner’s syndrome and in a patient with peripheral nerve injury.

Electron microscopic studies showed morphological alterations of peripheral nerve endings that are located in the border area of depigmented and clinically unaffected skin. Signs of axon degeneration were detected in dermal nerves in vitiligo skin that were not found in control skin. Immunohistologic studies of nerve endings in perilesional skin revealed abnormalities in the expression of nerve growth factors and neuropeptides (i.e. endogenous substances that are involved in nervous system functions). Blood levels of certain neuropeptides, such as β-endorphins and met-enkephalin, were increased among patients with active disease. In addition, communication between the nervous system and epidermal melanocytes has been demonstrated.

Several investigators have also provided biochemical support for this theory. The depigmented skin seemed to show abnormalities of the autonomic nerve system, an increased adrenergic tone and decreased parasympathetic tone. Furthermore, increased plasma levels of norepinephrine and increased urinary concentrations of catecholamine catabolites homovanillic acid and vanil mandelic acid were significantly associated with disease activity. These data indicated that catecholamine release, directly, or indirectly, could play a role in depigmenting process.

3. The self-destruct hypothesis

This theory suggests that precursors or metabolites of the melanogenesis are toxic to melanocytes. According to Lerner, melanocytes possess an intracellular protective...
mechanism to eliminate toxic melanin precursors (e.g. dopa, dopachrome, and 5.6 dihydroxyindole) and free radicals. In vitiligo, there might be a disturbance of this mechanism, leading to an accumulation of indoles and free radicals that are destructive to melanocytes.

This hypothesis is supported by clinical observations that hydroquinone derivatives like monobenzylether of hydroquinone are capable of causing chemical leukoderma. These chemicals probably disrupt the normal production of melanin, causing excessive production or leakage of toxic intermediates into the cytoplasm of melanocytes and subsequently cell lysis. Furthermore, vitiligo is more frequently seen on hyperpigmented skin areas following sun exposure, suggesting a correlation between enhanced melanogenesis and increased risk to develop vitiligo. There is also evidence that activation of the melatonin receptor leads to a dysregulation of the melanogenesis that finally results in a total destruction of melanocytes.

New insights in both the neuronal as well as self-destruct pathomechanism of vitiligo has been delivered by the group of Schallreuter. They suggested the central role of a defective pterin homeostasis in the process of melanocyte destruction. Tetrahydrobiopterin is an essential cofactor for the hydroxylation of phenylalanine to tyrosine via phenylalanine hydroxylase. In the affected skin, hydrogen peroxide levels are increased as a result of a defective tetrahydrobiopterin recycling and an increased monoaminooxidase activity, whereupon the detoxifying enzyme, catalase, is inactivated. Accumulation of breakdown products of pterin homeostasis (such as 6-BH4 and 7-BH4) that are cytotoxic to normal melanocytes, together with an increased hydrogen peroxide concentration and decreased catalase levels may all contribute to the destruction of melanocytes from the lesional epidermis of patients with vitiligo. In addition, serum levels of glutathione peroxidase, an enzyme that also plays a role in the degradation of hydrogen peroxide, was decreased in patients with longstanding vitiligo when compared with healthy controls. The novel treatment using topical pseudocatalase is based on these findings.

Another group found an abnormal antioxidant system in cultured melanocytes of patients with active vitiligo, indicating that vitiligo melanocytes are exposed to abnormal oxidative stress that can lead to cell injury and death. They suggested that the administration of compounds such as ubiquinone, vitamin E, selenium and methionine that is able to increase the level of the circulating and consequently of the epidermal antioxidant pool may play a therapeutic role among patients with active vitiligo. The effectiveness of antioxidants is currently being investigated.
4. Combination of 1, 2 and 3

It has been proposed that a combined theory rather than one separate theory is more appropriate in the etiology. Moreover, the finding that patients exhibit a variety of clinical forms and report different histories of onset of disease makes it tempting to believe that the etiology of vitiligo may vary among individual patients. A “convergence theory” postulated by Le Poole et al. in 1993, suggests that stress, accumulation of toxic compounds, infection, autoimmunity, mutations, altered cellular environment and impaired melanocyte migration and/or proliferation can all contribute to the phenomenon vitiligo.

Knowledge concerning the pathogenesis of vitiligo is accumulating fast. The identification of novel pathogenic mechanisms has also raised novel questions around the enigma. Although most investigators support the autoimmune hypothesis, there is also significant evidence that many other different endogenous as well as exogenous factors may contribute to the destruction of melanocytes in hair and skin. These findings may hopefully create new perspectives for the development of future therapeutic approaches for this disorder.

2.12 TREATMENT

In this section, a literature review is given on treatment strategies for the currently most applied active therapies, i.e. therapies directed to achieve repigmentation and stabilization of the lesions in vitiligo. Not all therapies are available in the Netherlands. No comment is given on the sequence to which treatment should be given in terms of effectiveness or side effects. The contents of this section provide essential background information for a better understanding of the studies performed in this thesis. Finally, some interesting novel therapeutic approaches will be discussed. Currently most applied therapies for vitiligo are presented in Table 5.
Table 5: Therapies for vitiligo

A. Nonsurgical repigmentation therapies
- Psoralen plus UV-A
- Narrowband UV-B
- Broadband UV-B
- Phenylalanine plus UV-A
- Khellin plus UV-A
- Corticosteroids

B. Autologous transplantation methods
- Minigrafting
- Thin split-thickness skin grafting
- Grafting of epidermal blisters
- Grafting of noncultured epidermal suspension
- Grafting of cultured epidermis/melanocytes

C. Depigmentation therapies
- Monobenzylether of hydroquinone (MBEH)
- Q-switched ruby (QSR) laser

D. Adjunctive therapies
- Sun protection
- Camouflage/self tanning agents
- Micropigmentation
- Psychological counseling

A. Nonsurgical repigmentation therapies

Psoralen plus UV-A (PUVA)

Psoralen photochemotherapy consists of the combined use of the photosensitizing chemical compound psoralen and ultraviolet radiation to induce a beneficial effect not produced by either alone. Psoralens are furocoumarin compounds, photo-dynamically-active drugs that are capable of absorbing radiant energy. A number of psoralens can be found in certain plant species, such as *Umbelliferae* (parsley, parsnip, and celery), *Rutaceae* (bergamot fruits, lime, gas plant, cloves, and citrus fruits) and *Moraceae* (figs). Many other psoralen derivatives are synthetically produced. The psoralens used in modern vitiligo treatment are methoxsalen or 8-methoxypsoralen, bergapten or 5-methoxypsoralen, trioxsalen or 4,5', 8-tri-methylpsoralen and unsubstituted psoralen (PS) (Figure 2). Worldwide, the most applied derivative is methoxsalen.
CHAPTER 2

Historical background. The use of psoralens as repigmenting agents was already described in ancient history. The Egyptians used an extract from the herbaceous plant *Ammi majus* that grows freely along the Nile delta. Old Indian literature describes the use of psoralen-

containing compound from *Ficus hispida* and *Psoralea corylifolia* plants. In 1947, Fahmy and Abu-Shady isolated three active crystalline compounds from the crude plant *Ammi Majus* that were all derivatives of coumarin. These were named *Ammoidin*, *Majudin* and *Ammidin* of which the chemical terms are 8-methoxypsoralen (or xanthotoxin or methoxsalen), 5-methoxypsoralen (or bergapten) and 8 isoamyleneoxypsoralen (or imperatorin) respectively. The first clinical trials in vitiligo using psoralens in combination with sunlight or ultraviolet (UV) rays were probably also performed in Egypt, by the dermatologist El Mofty in 1948. Patients were given the drugs on a daily dosage followed by exposure to sunlight or artificial UV rays. The use of artificial UV therapy alone to repigment vitiligo however, was already introduced by Montgomery in 1904, in the form of a Finsen light. Other investigators attempted to treat the disorder using a quartz lamp, Kromayer’s lamp or carbon arc lamp. In the 1960s, it was found that the action spectrum of psoralens was within the UV-A portion (320-400 nm) of the electromagnetic spectrum. The acronym PUVA (psoralens plus UV-A) was introduced in 1974 and refers to the use of oral psoralen with the (at that time) newly invented UV-A phototherapy units. To prevent cumulative phototoxic effects of UV exposure, treatments were given 2 to 3 times a week. With this regimen, the daily PUVA treatment had become obsolete.

**Mechanism of action.** The precise mechanism of stabilization and repigmentation of vitiligo lesions by PUVA therapy is unknown. Also the exact pathways in which psoralens in combination with UV-A radiation lead to photosensitization of the skin are yet to be

Figure 2. The chemical structures of unsubstituted psorale (A) and the psorale derivatives methoxsalen (B), trioxsalen (C), and bergapten (D).
elucidated. However, several studies have indicated that PUVA therapy is probably beneficial via a variety of complex mechanisms of which some are summarized below. After exposure of the skin to UV-rays the psoralens covalently bind to one or both strands of DNA and inhibit DNA synthesis by forming mono- and bifunctional photoadducts with interstrand cross-links between opposite thymidine base pairs\textsuperscript{221}. Light microscopic and ultrastructural studies have shown that PUVA stimulates hypertrophy (increase in size), proliferation and enzymatic activity of the melanocytes residing in the outer root sheath of hair follicles as well as melanocytes located at the margins of vitiliginous lesions\textsuperscript{222-225}. Repigmentation is therefore regarded as the result of the migration of these stimulated melanocytes into the depigmented skin areas. The mechanisms how these melanocytes migrate from the lower hair follicle to the epidermis are still being studied\textsuperscript{226}. Another study suggested that PUVA therapy may elicit the release of a certain melanocyte stimulating growth factor that is capable of stimulating melanocyte proliferation in vitiligo\textsuperscript{227}. It is also suggested that PUVA induced repigmentations are at least in part immunologically mediated\textsuperscript{228}. Investigators found that the so called “vitiligo associated melanocyte antigens”\textsuperscript{229} and antimelanocyte antibodies\textsuperscript{230} were decreased after a course of PUVA therapy.

Psoralens can be used either topically (topical PUVA) or orally (oral PUVA). As UV-source, the use of both artificial UV and natural UV (PUVASOL) has been described. Treatment regimens are found to differ between different institutes.

*Topical PUVA* is suitable for patients with “localized” vitiligo (according to Grimes et al., this refers to vitiligo with less than 20% depigmentation\textsuperscript{231}). Several psoralens have been used including methoxsalen, trioxsalen, PS and bergapten. Currently most popular is methoxsalen that is applied 30-45 minutes before exposure to natural or artificial sunlight. According to the treatment scheme of the “Vitiligo and Pigmentation Institute, Southern California, USA” \textsuperscript{231} one may start with 0.1% methoxsalen. When phototoxic reactions continuously occur, concentration may be lowered to 0.01%. When making use of a UV-A cabinet (lamps emitting 320-400 nm with a peak emission 365 nm) the start dose should be 0.12 J/cm\textsuperscript{2}, for all skin types. Dose can be increased 0.12 to 0.25 J/cm\textsuperscript{2} weekly according to skin type until minimal asymptomatic erythema (of the depigmented skin) occurs. The UV-A dosage is then maintained at quantity sufficient to retain minimal erythema reaction. Treatments are given once weekly.

When using natural sunlight instead of artificial UV-A cabinets, it is advised to use the 0.01% concentration. The treated vitiliginous areas are then exposed to sunlight for 30
minutes between 10 AM and 4 PM. If mild erythema has not occurred exposure time may be prolonged to 45 minutes.

Patients are to be informed that methoxsalen is a phototoxic drug and can very easily lead to severe erythema and blistering reactions of the skin. Also perilesional hyperpigmentation may occur, when the lotion is accidentally applied beyond the margins of the depigmented lesions. After UV exposure treated areas should be washed with water and soap.

In the Netherlands, 0.005% unsubstituted psoralen in 1% carbomer 934P gel can also be used as an alternative for methoxsalen.232

Oral PUVA can be applied for patients with generalized vitiligo. According to the guidelines of the American Academy of Dermatology, oral PUVA should not be given for children younger than 12 years.233 Four different psoralens have been used in the treatment of vitiligo in the following dosages:

- Methoxsalen: 0.3-0.6 mg/kg body weight
- Trioxsalen: 0.6-0.9 mg/kg body weight
- Bergapten and PS: 1.2 mg/kg body weight

Only methoxsalen capsules of 10 mg are available in the Netherlands. All drugs are ingested 1,5 to 2 hours before exposure to UV-A or sunlight.

When making use of a UV-A cabinet (lamps emitting 320-400 nm with a peak emission 365 nm) the start dose should be 0.5 J/cm², for all skin types. Dose can be increased 0.5 to 1.0 J/cm² weekly according to skin type until minimal lesional erythema occurs. The determination of the minimal phototoxic dose (MPD) is a more precise method to adjust the optimal dose.231 UV-A dosage is then maintained at a quantity sufficient to retain minimal lesional erythema reaction. In other centers, the start dose depends on the skin type (according to Fitzpatrick classification): I, 0.5 J/cm²; II, 1.0 J/cm²; III, 1.5 J/cm²; IV, 2.0 J/cm²; V, 2.5 J/cm²; VI, 3.0 J/cm². The dose is increased with 0.5-1.0 J/cm² with a maximum exposure between 8 and 12 J/cm².207

When using natural sunlight instead of artificial UV-A cabinets, the initial sun-exposure time should be 5 minutes. Exposure should be done between 10 AM and 4 PM. If mild erythema has not occurred exposure time may be prolonged with 5 minutes each time till the maximum of 45 minutes. In cases where oral psoralens are to be combined with sunlight, some clinicians prefer the use of trioxsalen, because of its lesser risk of phototoxic effects.220,231 Treatments are given twice to thrice weekly and never on two
consecutive days. UV blocking sunglasses should be worn till 8 hours after last intake of psoraleen and during the next day when exposed to natural sunlight. Patients are to be informed that methoxsalen is a phototoxic drug and can very easily lead to severe erythema and blistering reactions of the skin.

Absolute contraindications for PUVA therapy include history of previous side effects and/or phototoxic reactions related to oral PUVA therapy, concomitant use of photosensitizing medication, history of photosensitivity or photomediated disorders, skin type I, skin malignancy (in history), concomitant radio-, chemo- or immunosuppressive therapy, pregnant or lactating females (for oral PUVA), claustrophobia (when using artificial UV-A cabinet), “lip-tip” and/or mucosal vitiligo, and a cumulative UV-A dose of higher than 1000 J/cm² (for oral PUVA). Relative contraindications are ineffectiveness of previous treatment with PUVA, patients younger than 12 years (for oral PUVA), skin type II, and high patients’ burden for the therapy.

Short-term cutaneous side effects of PUVA therapy are increased contrast formation between normal pigmented skin and lesional skin, phototoxic reactions (from erythema to blisters and burns), pruritus, xerosis cutis, and Koebner phenomenon. Short-term systemic side effects are only observed with oral PUVA and may include nausea, vomiting, mild epigastric discomfort, headaches, dizziness, (transient) elevation liver function tests, insomnia, nervousness, fatigue, and drowsiness. Side effects that are associated with the long-term use of PUVA therapy have also been described. Most commonly reported are lichenification, desquamation, telangiectasia, lentigines or freckles, leukoderma punctata, aging, wrinkling, and skin malignancies. Cataract is a long-term side effect that is related only to the use of oral PUVA. The major advantages of topical applied psoralens followed by UV-A irradiation over oral PUVA therefore include lower required UV-A doses and lack of systemic and ocular toxicity.

Because of the possible long-term side effects, pre-treatment diagnostic tests include liver and renal function tests and ophthalmologic examination that should be repeated annually.

Narrowband UV-B

In the late 80's, ultraviolet lamps with a peak emission around 311 nm (TL-01, Philips, Eindhoven, The Netherlands) have been introduced successfully for the treatment of psoriasis and constitutional eczema. More recently, this narrowband UV-B therapy has also been applied as a repigmentation therapy of patients with generalized vitiligo.
Mechanism of action. The mechanisms of UV-B-induced repigmentation in vitiligo are unknown. Because in patients with vitiligo, local and systemic abnormalities of the cellular and the humoral immunity are found, stabilization of the disease can be explained by the well known immunomodulating effects of UV-B-radiation\textsuperscript{235}. It is also likely that narrowband UV-B, similar to PUVA therapy, stimulates the melanocyte reserves in the hair sheaths, because repigmentation was also found to occur in a perifollicular pattern and was not observed in lesions with white amelanotic hairs\textsuperscript{232}. Further investigations should be conducted to elucidate the mechanisms of action of narrowband UV-B therapy in vitiligo.

Treatment regimen. In the Netherlands Institute for Pigmentary Disorders, narrowband fluorescent tubes (Philips TL-01/100 W) with an emission spectrum of 310 to 315 nm and a maximum wavelength of 311 nm are used for this therapy. The start dose is 250 mJ/cm\textsuperscript{2} (for all skin types) that is increased with 10-20\% until minimal erythema occurs in the depigmented areas. Because some parts of the body may reached minimal erythema faster (such as the face) than others, a differential dosimetry per body region may be needed during the session. Treatment frequency is twice weekly and never on two consecutive days.

The advantages of narrowband UV-B over oral PUVA therapy include shorter treatment times, no oral drugs required (no systemic effects), absent drug costs, less burning incidents, no hyperkeratosis seen after long-term irradiation, less contrast formation between depigmented and normal pigmented skin, no need for post-treatment eye

Figure 3. (A) Relative spectral energy distribution of the Philips TL-01 (Narrowband UV-B) fluorescent lamp. (B) Relative spectral energy distribution of the Philips TL-12 (Broadband UV-B) fluorescent lamp.
photoprotection, safe use in children and pregnant women\textsuperscript{232,236}.

Absolute contraindications for narrowband UV-B therapy include history of previous side effects and/or phototoxic reactions related to narrowband UV-B therapy, concomitant use of photosensitizing medication, history of photosensitivity or photomediated disorders, skin type I, skin malignancy (in history), concomitant radio-, chemo- or immunosuppressive therapy, claustrophobia, patients younger than 6 years, "lip-tip" and/or mucosal vitiligo. Relative contraindications are ineffectiveness of previous treatment with narrowband UV-B or other forms of photo(chemo)therapy, pregnant or lactating females, skin type II, and high patients' burden\textsuperscript{232,236}.

Short-term side effects may include warmth sensation of the face 4-6 h after therapy, herpes labialis, eczema herpeticum, pruritus, and xerosis cutis\textsuperscript{232,237,238}. Long-term side effects of narrowband UV-B have not yet been observed in patients with vitiligo (see section "Long-term carcinogenic risks of photo(chemo)therapy in vitiligo").

**Broadband UV-B**

The results of this phototherapeutic modality in the treatment of vitiligo were first reported in 1990, by Köster and Wiskemann\textsuperscript{239}. Surprisingly, no phototoxic reactions were observed. However, caution is needed during the UV-B dose increments because it is known that shorter wavelengths are responsible for erythema formation in the skin (Figure 3). The mechanisms of action of broadband UV-B in vitiligo are unknown (see also section "Narrowband UV-B")

*Treatment regimen.* According to the German study, broadband fluorescent tubes (Philips TL-12, Westinghouse FS, Waldmann UV-6 or UV-21) with an emission spectrum of 290 to 320 nm can be used\textsuperscript{239}. The start dose is 20 mJ/cm\textsuperscript{2} (for all skin types) and should be increased with 20% until lesional minimal erythema occurs. Patients are treated twice to thrice weekly, and not on two consecutive days. Absolute and relative contraindications are similar to those suggested for narrowband UV-B.

Short-term side effects may include erythema, pruritus, and xerosis cutis\textsuperscript{239}. Long-term side effects of broadband UV-B have not yet been observed in patients with vitiligo (see section "Long-term carcinogenic risks of photo(chemo)therapy in vitiligo").

**Phenylalanine plus UV-A**

Phenylalanine is one of the essential amino acids and its L-form is easily available in nature. It constitutes an essential part of daily dietary proteins. It has been observed that
normal melanogenesis occurs in phenylketonuria (PKU) skin after the administration of tyrosine followed by UV-A exposure\textsuperscript{240}. Tyrosine is a known precursor of melanin. In the 80s, Cormane and co-workers also tried the same regimen in vitiliginous skin but could not observe any clinical results. However, in 1985, the same group managed to induce evident signs of repigmentation in patients with vitiligo, using another amino-acid, L-phenylalanine (also in combination with UV-A irradiation) that is also a precursor of melanin\textsuperscript{241}.

**Mechanism of action.** Proposed mechanisms of repigmentation include stimulation of melanocyte activity and melanosome formation\textsuperscript{242}, a shift in the HLA-DR+ OKT6+ Langerhans’ cell population that results in a modified control of immune responsiveness to certain antigens\textsuperscript{243}, or an inhibition of antibody synthesis\textsuperscript{244}. L-phenylalanine has not been shown to have phototoxic or genotoxic properties. In the clinical trials, an increased tolerance for sunburns was reported in some patients with vitiligo\textsuperscript{241}.

**Treatment regimen.** L-phenylalanine is given in a dose 100 mg/kg body weight 1.5 to 2 hours before exposure to UV-A or sunlight. When the patient experiences nausea after ingestion, the dose can be decreased to 50 mg/kg body weight (scheme “Department of Dermatology, Academic Medical Center, Amsterdam, The Netherlands”)\textsuperscript{241}. UV-A emitting lamps can be used with a spectrum of 320 to 400 nm and a peak emission around 365 nm. The start dose should be 2 J/cm\textsuperscript{2} multiplied with the skin type. The dose can be increased with 20\%, with a maximum increment of 1 J/cm\textsuperscript{2} per treatment until lesional minimal erythema occurs. The frequency of treatment is twice weekly and not on two consecutive days.

Absolute contraindications include phenylketonuria, pregnant or lactating females, history of previous side effects and/or phototoxic reactions related to phenylalanine, concomitant use of photosensitizing medication, history of photosensitivity or photomediated disorders, skin type I, skin malignancy (in history), concomitant radio-, chemo- or immunosuppressive therapy, claustrophobia, patients younger than 6 years, “lip-tip” and/or mucosal vitiligo\textsuperscript{241}. Relative contraindications are ineffectiveness of previous treatment with phenylalanine plus UV-A therapy, or other forms of photo(chemo)therapy, abnormal liver and renal functions, severe cardiovascular disease, skin type II, and high patients’ burden.

Reported short-term side effects are erythema, pruritus, and xerosis cutis and mild nausea after oral ingestion of the drug. Possible long-term side effects are unknown.
Khellin plus UV-A

Khellin (4,9-dimethoxy-7-methyl-5H-furo [3,2-g]-1 benzopyran-5-one) is a furanochromone with a chemical structure resembling that of psoralens (Figure 4). The substance was used in the past (1940s and 1950s) as a vasodilator in the treatment of angina pectoris and asthma. An oral dose of 50 to 100 mg is given 2.5 hour before exposure to UV-A. UV-A doses range from 5 to 15 J/cm², depending on the skin type.

In contrast to PUVA, khellin does not cause phototoxic erythema reactions and has a low genotoxic potential because of its induction of only monofunctional photoadducts. Temporary elevations of liver enzymes have been reported among patients receiving oral khellin. However, evident liver damage has not been observed yet. Khellin can also be applied in a 2 to 3% liquid base (lotion) or in a 5% cream (o/w) base, 1 hour before exposure to UV-A or sunlight. The mode of action of khellin in repigmenting vitiliginous lesions is unknown. Repigmentation also occurred in a perifollicular pattern.

Absolute contraindications include history of previous side effects and/or phototoxic reactions related to oral khellin plus UV-A therapy, concomitant use of photosensitizing medication, history of photosensitivity or photomediated disorders, skin type I, skin malignancy (in history), concomitant radio-, chemo- or immunsuppressive therapy, pregnant or lactating females (for oral khellin), claustrophobia (when using UV-A cabinet), abnormal renal- and liver functions (for oral khellin), cataract, patients younger than 12 years, “lippi” and/or mucosal vitiligo. Relative contraindications are ineffectiveness of previous treatment with khellin plus UV-A or other forms of photo(chemo)therapy, cardiovascular diseases (angina pectoris and hypertension), skin type II, and high patients’ burden.

Reported short-term side effects are pruritus, xerosis cutis. If khellin is is taken orally mild nausea, (transient) elevation of liver transaminases may occur. Possible long-term side effects are unknown.

Long-term carcinogenic risks of photo(chemo)therapy in vitiligo

In patients with psoriasis, long-term PUVA therapy was found to be associated with an increased risk for skin cancer, especially squamous cell carcinoma (SCC). Based on
epidemiological data, a statistically increased incidence of nonmelanoma skin cancer has been observed in those patients who had received a cumulative UV-A dose exceeding 1000 J/cm². More recently, Stern et al. also found the risk of melanoma to be increased among those receiving at least 250 PUVA treatments. These findings are concerning but remarkably, a similar increased risk for these skin cancers has not been documented among patients with vitiligo. Harrist et al. in 1984 reported 5 cases with actinic keratoses in 230 patients with vitiligo treated with oral PUVASOL for a period between 22 and 55 months with a follow-up period of 55 months after therapy. No cases of skin cancer could be detected. The group of Lassus followed up 139 patients with vitiligo for 1 to 5 years after receiving oral PUVA therapy. In 3 cases, actinic keratoses was diagnosed, however, there was no report on malignant skin lesions. In a 10 year follow-up study Abdullah et al. were not able to detect any skin cancers in 23 patients with vitiligo who had received prolonged PUVA therapy. Wildfang and co-workers published in 1992 the results of a retrospective study on 59 patients with vitiligo who had received oral (indoor) PUVA therapy between 1972 and 1986. Again, no skin abnormalities could be found among the treated patients. Another study in the USA failed to document, after a follow-up period of 4 years, any skin malignancies in 326 patients with vitiligo who had received oral PUVA for at least 4 months in the period 1977 to 1988.

To date, only two patients with vitiligo have been reported with squamous cell carcinoma occurring on sun-exposed depigmented skin areas after prolonged PUVA therapy. It was striking that in both cases, the cumulative dose did not exceed the maximum recommended dose of 1000 J/cm² in the first and 392 J/cm² in the second case. Moreover, in the first case, the time between the start of oral PUVA therapy and the development of the skin cancer was only 3 years which is relatively short for tumor-induction in general. These two patients may have suffered from a defective DNA-repair mechanism and/or an abnormal immune surveillance, however these factors were not investigated in these reports. Furthermore, only rare anecdotal cases have been reported of nonmelanoma skin malignancies occurring in the depigmented or in the normal skin of untreated patients. The patients described were all over 60 years old. Melanomas are not expected to occur within vitiligo lesions because their cell of origin is absent. However, in absence of epidermal melanin, one would expect an increased incidence of nonmelanoma skin cancers, such as basal cell carcinoma or squamous cell carcinoma. It is therefore surprising that in vitiliginous skin in comparison with the normally pigmented skin of caucasians from Northern Europe, fewer sunburn cells
were observed after UV exposure\textsuperscript{266}. A histologic study in 1987 among 27 patients with longstanding vitiligo could not detect an increased incidence of actinic damage in the sun-exposed areas of both vitiliginous skin and normally pigmented skin\textsuperscript{267}.

The relatively low incidence of skin cancer among patients with vitiligo may at least be partly explained by some medical and behavioral factors\textsuperscript{17}. In contrast to psoriasis patients, patients with vitiligo receive lower cumulative PUVA dosages and do not use tar preparations, cystostatic drugs (methotrexate) or immunosuppressive drugs (cyclosporine). It is also known that many patients with vitiligo apply sunscreens with a high protection factor, wear appropriate clothing (such as long sleeves) or stay indoor as much as possible to protect the depigmented skin against sunburns. Some patients even avoid taking sunny holidays. Unlike psoriasis patients, they show less tendency to expose themselves to extra sunrays during the day or to take Dead Sea spas\textsuperscript{50,268}. Reports on skin cancer among patients with vitiligo living in tropical countries (such as Africa, Asia or South America) are also sparse. This cannot be entirely attributed to the use of sunscreens or indoor activities. Compared with those patients living in the western countries, many of these patients have a lower economic status. Sunscreens are costly for most of them. Many of these patients do not have indoor jobs and work mostly on farms or as outdoor workers and are therefore exposed to intense sunrays. In contrast, it is known that albino patients, who are also characterized by lack of melanin in the skin, do show an increased risk for developing skin cancers, especially those living in sunny regions\textsuperscript{269-271}. Based on these observations some investigators suggest that the depigmented skin of patients with vitiligo, despite the lack of melanin, is able to develop some kind of resistance against the harmful effects of sunlight\textsuperscript{17}. A Danish study indicated that hyperkeratosis in vitiligo skin offered as efficient photoprotection as did the normal stratum corneum in pigmented skin\textsuperscript{272}. More studies are needed to explain these phenomena and to elucidate whether other compensating mechanisms may operate in the vitiligo skin.

The long-term carcinogenic risk of photochemotherapy with khellin is believed to be less than that with psoralens\textsuperscript{245} . Khellin forms monofunctional adducts and cross links with DNA with a maximum action spectrum at 360 nm\textsuperscript{246}. However, khellin predominantly forms monoadducts and the induction of cross-links requires fluences of up to 100 times more than needed for the formation of cross links with methoxsalen. Compared with methoxsalen, khellin is a very weak producer of reactive oxygen species\textsuperscript{247}. To date, no cases of skin cancer related to the use of khellin photochemotherapy have been reported.

Broadband and narrowband UV-B therapy are being used for the treatment vitiligo since the early 90s. In mouse experiments, UV-B has been shown to have carcinogenic
properties\textsuperscript{273-275}. There are presently still insufficient (epidemiological) data available in humans to provide evidence-based advice regarding a safe maximum dose. According to a dose-response model it has been calculated that long-term narrowband UV-B therapy may carry less risks for skin cancer than PUVA therapy\textsuperscript{276}. In daily clinical practice, some precautions can be undertaken to minimize the risk of cancer induction by photo(chemo) therapy. Firstly, the "skin saving principle" can be applied; parts of the body where no lesions are present (especially the face) should be shielded during treatments. Also parts that have repigmented satisfactorily should, if possible, be shielded during next treatments (for example by wearing trousers). Genitals should also be shielded, because genital tumors have also been observed after PUVA therapy\textsuperscript{277} and because these areas as a rule, do not respond to photo(chemo)therapy\textsuperscript{207}. Other safety measures include the prevention of unnecessary exposure to natural sunlight on both treatment and nontreatment days and the use of UV-blocking agents on sun-exposed areas. Until more epidemiological data becomes available, we suggest that in the meantime, recommendations for vitiligo patients regarding safe maximum cumulative PUVA doses and safe maximum number of UV-B treatments should follow those advised for psoriasis patients, i.e. 1000 J/cm\textsuperscript{2} \textsuperscript{261} and 300 treatments \textsuperscript{278}, respectively.

Corticosteroids

Tsukada probably wrote the first publication on the use of corticosteroids in vitiligo in 1959. By employing local injections of corticosteroids, the investigator observed repigmentation in the lesional areas\textsuperscript{279}. Farah et al. in 1967 \textsuperscript{280} reported an enhanced effectiveness of oral psoralens when combined with daily ingestion of 8 to 12 mg triamcinolone acetonide. In the years thereafter, several publications followed that report on the effectiveness of corticosteroids in vitiligo. The corticosteroids were administered in different ways; topically, intralesionally and orally. Low, mid and high potency preparations have been used.

The mechanism of action of corticosteroids in vitiligo is unclear. It is often assumed that corticosteroids suppress inflammatory processes that are frequently observed in active progressing lesions\textsuperscript{281}. The use of oral corticosteroids was associated with decreased serum levels of antimelanocyte antibodies among patients with active vitiligo\textsuperscript{282,283}. It is not known whether the corticosteroids used in the clinical studies in vitiligo have a direct stimulating effect on melanocyte division and migration. Furthermore, it is striking that the best results are achieved on sun-exposed areas (such as face and neck). Both perifollicular as well as perimarginal repigmentation patterns can be seen with
corticosteroids. Because most studies were not controlled, (unintentional) UV exposure may also have contributed to the repigmentations associated with the use of these corticosteroids.

The following topical drugs have been tested in clinical trials. The corticosteroid is applied once to twice daily on the vitiliginous patches.

- 0.1% triamcinolone acetonide
- 0.01% fluocinolone acetate
- 0.1-0.2% betamethasone valerate
- 0.05% halomethasone
- 0.05% fluticasone propionate
- 0.05% clobetasol propionate

Triamcinolone acetonide (10 mg/ml) is the drug of choice in the intralesional administration of corticosteroids. The drug is injected in 2 cc dosage once weekly for 5 weeks.

Corticosteroids can also be given orally, in particular to those patients with rapid progressive disease. To minimize systemic side effects, different dosage schemes have been tried in vitiligo (Table 6).

Table 6. Oral corticosteroid therapy. Treatment regimens

<table>
<thead>
<tr>
<th>Corticosteroids daily dosage</th>
<th>Author, year</th>
</tr>
</thead>
<tbody>
<tr>
<td>methylprednisolone, 10-15 mg dd.</td>
<td>El Mofty, 1974</td>
</tr>
<tr>
<td>prednisolone 5 mg / betamethasone 0.5 mg / paramethasone acetate 2mg / methylprednisolone 4 mg</td>
<td>Imamura, 1974</td>
</tr>
<tr>
<td>adult: 1 dd. 3-5 tab / child: 1 dd. 0.5 tab &gt; 3 months half dose ; max 6 months</td>
<td></td>
</tr>
<tr>
<td>low dose prednisolone first 2 months: 7.5-20 mg dd. (or 0.3 mg/kg body weight) 3rd month: half of start dose 4th month : half of dose 3rd month</td>
<td>Moon, 1999</td>
</tr>
</tbody>
</table>

Oral minipulse therapy

| Author, year |
|-----------------------------|--------------|
| dexamethasone 0.5 mg ± betamethasone 0.5 mg | Pasricha, 1993 |
| 10 tablets on 2 consecutive days, repeat weekly min. 5 weeks / max 25 weeks | Kanwar, 1995 |
Local side effects include dermatitis perioralis, contact dermatitis, rosacea-like or acneiform eruptions, irritative reactions, pruritus, burning sensations, folliculitis, delayed wound healing, skin infections, skin atrophy, telangiectasia, striae, hypertrichosis, purpura, and bleeding tendency. The risks of local side effects are increased when the drug is applied under occlusion, or applied on the face, on the genital area and on the body folds (axilla, groin, elbow- and knee folds) or when injected intralesionally.

Systemic side effects occur very rarely with the local application of corticosteroids. Side effects that are reported in patients with vitiligo using oral corticosteroids are; Cushing syndrome, weight gain, gastro-intestinal distress, abdominal pain, increased appetite, insomnia, dizziness, diarrhea, irregularity of menstruation and frequent urination. These side effects are reported to be minimal and temporary.

**B. Autologous transplantation methods**

In general, autologous transplantation methods are only indicated after medical treatment has failed. These methods can be used in combination with medical and/or irradiation therapies. Transplantation may also be considered as first option to treat patients with stable and/or focal (segmental) vitiligo. Autologous transplantation of melanocytes should not be regarded as a causal therapy. Even after a successful grafting, depigmentation of the grafts may still occur when reactivation of the disease takes place.

The general selection criteria for autologous transplantation methods are:
1. Resistancy for medical therapy
2. Stable vitiligo
3. Absence of the Koebner phenomenon
4. Positive minigrafting test
5. No tendency for scar or keloid formation
6. Patients are older than 12 years

**Minigrafting**

*Method.* Two-mm full thickness punch grafts are harvested from normally pigmented donor sites (such as the hip, buttocks and outer thigh) and are subsequently transplanted to depigmented acceptor sites in which similar punched out skin had been removed. The grafts are placed 5 mm to 8 mm apart, and are covered with a transparent adhesive tape.
Extremities are also covered with an elastic bandage for one week to give compression and fixation on the grafted site. Subsequently, grafted areas are irradiated with UV-A (10J/cm²) twice a week, to promote the outgrowth of pigment cells from the minigrafts. The procedure can be performed under local infiltration anesthesia. A facial tanner or a sunbed can be used as the UV-A light source that can be performed at home. Pigment can be observed concentrically migrating, though within a maximum diameter of 8 mm, from the grafts into the depigmented skin, within 8 weeks following transplantation.

Complications at donor site may include light scarring, postinflammatory hyper- or hypopigmentation, and infection. At the recipient site cobblestone effect, variegated appearance of the grafts, sinking pits, and infection have been observed as adverse effects.

Thin split-thickness skin grafting

Method. One to two hours prior to the procedure, patients apply a local anaesthetizing cream EMLA®, containing lidocaine 25 mg/g and prilocaine 25 mg/g eutectic mixture, to both donor and recipient areas. The cream should be applied to the skin in a thick layer, under occlusion of a transparent adhesive foil. After the EMLA® cream is wiped off, a needle pinprick test is performed to ensure that a satisfying degree of anesthesia is achieved in both donor and recipient sites. The recipient area is dermabraded with a diamond burr until uniform pinpoint capillary bleeding was seen. A very thin split-thickness epidermal graft (0.1 to 0.15 mm thick) is then removed from a normally pigmented donor area (usually the hips or buttocks) with an electrically driven dermatome. The base plate chosen determines the width of the cut required. As an alternative, the same dermatome can also be used to remove the lesional recipient skin, instead of dermabrasion. The length of the skin graft depends on the length of the dermabraded or shaved achromic area. The maximum size of the grafts is about 150 cm². The graft is gently placed onto the dermabraded achromic areas. The surface is flattened and stretched over the dermabraded area using the flat longitudinal side of a pair of surgical tweezers. By doing this, residual wound exudate and small blood clots present underneath the graft, can be removed to optimize graft take. Donor areas are covered with dry sterile gauzes and an adhesive foil. Wound dressings of the recipient area consist of sterile suture strips, sterile gauze impregnated with an antibiotic, dry sterile gauze and adhesive bandage. Treated extremities are covered with an elastic bandage to secure light compression and immobilization. After removal of the wound dressings after two weeks, the grafted area and the donor site can be irradiated with UV-A twice weekly, to promote repigmentation.
At the donor site, light scarring, postinflammatory hyper-or hypopigmentation, and infection may occur as adverse effects. Milia, hematoma, thick graft margins, wrinkles in the graft, and infection are possible complications at the recipient site.

Grafting of epidermal blisters

Method. For this method, a suction blister apparatus is essential that is capable of exerting 200 mm Hg negative pressure to separate the epidermis from the dermis at the normally pigmented donor skin. Two days before transplantation, blistering of the depigmented lesion is induced using liquid nitrogen or topical psoralens plus UV-A therapy. After blister formation, the depigmented epithelium is removed and the roofs of the pigmented donor blister are grafted to the denuded lesional areas.

Scarring does not occur at the donor site. Infection is sometimes seen at the recipient site.

Grafting of cultured autologous melanocytes

Method. During this procedure, autologous melanocytes are expanded by in vitro culturing techniques and transplanted into a previously denuded achromic skin area. This is an expensive technique that requires special laboratory expertise. However, it may represent an adequate method to repigment larger vitiliginous skin areas in the future. There are several methods to obtain cultured autologous melanocytes.

a. Grafting of pure melanocytes

Autologous melanocytes are grown for a period of four weeks in a special medium containing 12-O-tetradecanoyl-phorbol 13-acetate (TPA), cholera toxin (CT) and isobutylmethylxanthine (IBMX). Then suction blistering is performed in the recipient achromic sites. The cultured melanocytes are then injected into the blister cavities. Using this method, Lerner et al. in 1987 observed a satisfying degree of repigmentation in two patients with piebaldism. Because TPA is a potent tumor promoter, the safety of this medium remains questionable. Therefore culturing of melanocytes in physiologic reagents is highly recommended, but this is very expensive.

b. Grafting of melanocytes mixed with keratinocytes

Autologous melanocytes and keratinocytes are mixed cultured on a collagen-coated membrane for 2 weeks. The membrane is then transplanted into dermabraded or liquid nitrogen denuded vitiliginous skin. After 1-2 week the collagen membrane detaches from
the graft spontaneously. Repigmentation in the graft gradually occurs from 2 to 6 months after the day of transplantation. A major advantage is that TPA or choleratoxin is not required. In mixed cultures, the essential melanocyte growth factors are provided by the keratinocytes. In some cases, the treated skin area appears lighter than the normal pigmentation because the number of the grafted melanocytes is too low. The recipient area may also show light hypertrophic scarring or atrophy.

At the donor site, slight scarring, postinflammatory hyper-or hypopigmentation, and infection can be observed as possible adverse effects. The recipient site is sometimes complicated by improper color matching and infection.

Grafting of noncultured melanocyte suspension

More simplified methods of grafting of fresh epidermal cell suspensions bearing melanocytes have also been successfully used to repigment vitiligo macules. After trypsinization of a shave biopsy taken from the occipital area, Gauthier and Surleve-Bazeille injected the suspension containing keratinocytes and melanocytes into liquid nitrogen blisters induced within the vitiligo macules. Olsson and Juhlin modified the technique in 1998. They took a shave biopsy from the buttocks, separated the cells and concentrated the melanocytes in vitro. The final suspension, containing the basal layer and the about half of the stratum spinosum, was subsequently applied to dermabraded vitiliginous areas with a size eight to ten times larger than the donor area.

Slight scarring, postinflammatory hyper-or hypopigmentation and infection may complicate the donor site. Improper color matching, and infection can be sometimes seen at the recipient site.

C. Depigmentation therapy

For patients with extensive areas of depigmentation (more than 80%) and/or disfiguring lesions on the face, who do not respond to repigmentation therapies, depigmentation of the residual melanin should be considered. These patients should be informed that bleaching or removal of the remaining pigmentation may be a permanent and irreversible process. During and upon completion of the therapy, patients are permanently at risk for acquiring sunburn from acute solar irradiation. Patients must therefore be advised to minimize sun exposure and to apply broad-spectrum sunscreens.
Bleaching agents

In the late 1930s, it was observed that tannery workers who used a new type of rubber gloves developed irregular confetti-type depigmentations. The areas of pigment loss were most obvious in dark-skinned people and were most prominent on the hands and forearms (areas in contact with the gloves). It later appeared that the rubber gloves contained monobenzylether of hydroquinone (MBEH) that was used as an antioxidant to prevent the aging of rubber. Subsequently, this compound was used to treat several disorders of hyperpigmentation. Because of the side effects encountered with this drug, MBEH is nowadays only applied to remove residual melanin in patients with vitiligo universalis. MBEH is a potent melanocytotoxic agent. The modes of actions are diverse and are well-summarized elsewhere. Loss of pigment can also occur at distant sites of application. The mechanism behind this phenomenon is unclear.

The treatment should start with a single daily application to a test spot. If no adverse reactions occur, greater skin areas can be gradually treated in a frequency once to twice daily. It normally requires 1 to 3 months to initiate response. Depending on the percentage of the residual pigmentation, 6 months to 2 years may be required to complete the therapy. Patients must avoid direct contact of the treated area with untreated skin or with normal pigmented skin of other individuals (partners) for at least 2 to 3 hours after application of the cream. During and upon completion of the therapy, patients are permanently at risk for acquiring sunburn from acute solar irradiation. Relapses may occur even after complete depigmentation, especially after sun exposure. Patients must therefore be advised to minimize sun exposure and to apply broad-spectrum sunscreens.

In the Netherlands, 4-methoxyphenol (monomethyl ether of hydroquinone or 4-hydroxyanisole) in a 20% cream can be used as an alternative for MBEH (Figure 5).

Figure 5. The chemical structures of monobenzylether of hydroquinone (A) and monomethylether of hydroquinone (4-methoxyphenol) (B).
Absolute contraindications for the use of MBEH include no previous attempts for repigmentation in history, depigmentation of less than 80% of the body surface, previous side effects and/or allergic reactions to bleaching agents in history. Relative contraindications are previous insufficient response to bleaching agents, patients younger than 18 years, pregnant or lactating females, and high patient's burden.

Short-term side effects are (contact) dermatitis, pruritus, corneal and conjunctival melanosis. At long term, leukomelanoderma en confetti, and exogenous ochronosis may occur as adverse effects. These long-term effects have not yet been reported in patients with vitiligo universalis.

Laser therapy

Another form of depigmentation therapy for vitiligo has also been developed, making use of a Q-switched ruby (QSR) laser apparatus. The QSR laser beam with a wavelength of 694 nm is capable to selectively destroy melanin and melanin-containing structures in the skin. As a result, the risk for scar formation is minimal.

One should start with a test spot and should not treat all the residual pigment in one session. The test spot is evaluated after 2 months. If there is no response, further laser therapy should be discouraged. If evident depigmentation occurs, the treatment can be continued until total depigmentation is observed. When the treatment is experienced to be too painful it can be performed under local anaesthesia. To prevent sunburn and risk of relapse, the use of broad-spectrum sunscreens should be advised when the skin is exposed to sunlight.

Absolute contraindications include no previous attempts for repigmentation in history, depigmentation of less than 80% of the body surface, negative Koebner phenomenon, and tendency for hypertrophic scar or keloid formation. Relative contraindications are previous insufficient response to laser therapy, patients younger than 18 years, and high patient's burden.

Short-term side effects are pain, blistering, pinpoint bleeding, and swelling. These effects are all transient of nature. Long-term side effects are rarely observed and may include hypertrophic scarring or keloid formation.
D. Adjunctive “therapies”

The following are not really “therapies” but may help the patient to better cope with the physical, cosmetical and emotional effects related to the loss of pigment in the skin.

Sun protection
The use of broad-spectrum sunscreens are recommended not only to decrease the risk for acquiring sun burn, but also to limit contrast formation between vitiliginous skin and normally pigmented skin.

Camouflage and self-tanning agents
Cosmetics and stains can be used to camouflage limited areas of depigmented skin. These products however, may be rubbed off and may stick to clothes. Self-tanning preparations containing dihydroxyacetone yield a yellow color of the stratum corneum. This modality can also be useful in some patients.

Tattooing (Micropigmentation)
Using this method, iron-oxide pigment is implanted dermally into the lesion. The lips, nipples, and distal extremities (wrists, distal digits) are suitable sites. A perfect color match of the implanted pigment is difficult to obtain, mostly because of seasonal depending color variations of the nonlesional skin. Moreover, the Tyndall effect gradually alters the implanted color. Patients are to be informed that the artificial pigment does not protect the skin against sunburn. The choice to treat a lesion with micropigmentation should be made with caution. If the implanted color fails to match, it is difficult to remove the artificial pigment; laser therapy was previously not shown to be effective.
Complications of this method may include (herpes labialis) infections, allergic reactions and koebnerization.

Psychological counseling
Many patients with vitiligo are emotionally distressed by the loss of pigment in the skin. Therefore psychological counseling may be considered. Regular meetings organized for patients with vitiligo may enhance acceptance of the disease and coping mechanisms. It is noteworthy that many countries have founded vitiligo support groups.
E. Novel therapeutic approaches

Fluticasone propionate plus UV-A therapy

A recent study have shown that a combination therapy using a potent corticosteroid (fluticasone propionate) applied once daily and UV-A irradiation (10 J/cm²) performed twice weekly, is an effective and a safe method to repigment localized vitiligo lesions\textsuperscript{288}. The combination therapy led to a higher percentage of repigmentation than either fluticasone propionate or UV-A alone. Perifollicular and marginal repigmentation could be observed as fast as 6 weeks after the start of therapy in both adult and pediatric patients. After 9 months of therapy, clinical and histologic examinations revealed no signs of atrophy or telangiectasia in the treated skin. A major benefit of this modality is that it can be easily performed at home, using a UV-A tanning equipment (e.g., a facial tanner) as the light source\textsuperscript{288}. A longer follow-up period is needed to establish whether the corticosteroid-induced repigmentation is permanent.

Focussed microphototherapy

The clinical effects of focussed microphototherapy have been studied since 1990 by a group of investigators in Milan, Italy\textsuperscript{319}. For this form of phototherapy, UV-B light with a spectrum of 280-315 nm is used. The skin is prepared by application of water and glycerin to facilitate the penetration of the UV-B rays in the skin. Subsequently, a dark pad with 2-mm holes is applied to the skin. The light is shined through the holes and causes a mild to moderate burn on the skin. Treatments are given daily for a week and thereafter several times weekly or twice a month. In addition, the therapy requires a highly advanced computer program and a videocamera to control and to monitor the UV-B delivering equipment. The results of the studies showed that the more frequent the treatments, the more rapid the pigment returns. About 25% of the patients have excellent result having most of their pigment back, whereas 50% has only moderate repigmentation. As with other forms of photo(chemo)therapy, acral sites of the body reveal a poor response.

It is regarded a major advantage that using the focussed microphototherapy, only the depigmented skin can be treated so that unaffected skin areas are not unnecessarily exposed to UV-B irradiation. By this way, contrast formation between the depigmented and the normal pigmented skin can be avoided. However, the therapy requires expensive equipment and trained personnel and will therefore not be available for many patients around the world.
Pseudocatalase plus UV-B therapy

Based on results of oxidative stress and calcium dysregulation in vitiligo, a substitute for depleted catalase together with calcium, a new topical treatment modality has been developed. A low molecular weight manganese complex (MW 328) has been synthesized with functions effectively to remove hydrogen peroxide from the patients. Intracellular matrix concentrations of calcium are adjusted with $10^{-2}$M calcium chloride. Therapy involves a twice-daily application of the pseudocatalase cream and a suberythemal dose of UV-B light twice a week. The treatment yielded more than 90% repigmentation of hands and face in a pilot study with 33 patients\textsuperscript{201}. However, this study was uncontrolled and it is unknown whether the observed repigmentations should be attributed to pseudocatalase alone or to the combination of the substance with UV-B therapy or to UV-B therapy alone.

Systemic antioxidant therapy

Based on the antioxidant theory, a clinical trial is being performed in Italy using the oral administration of compounds such as ubiquinone, vitamin E, selenium and methionine\textsuperscript{203,204}. It is unknown whether this trial has included a placebo group. The rationale to use these substances for vitiligo is controversial; antioxidants are also used as alternative forms of therapy for a variety of disorders, whereas their mechanism of action is unknown and probably nonspecific. Moreover, these drugs are relatively expensive and are not reimbursed by health insurance companies.

Treatment with Suplatast Tosilate (IPD)

An anti-allergic drug, "Suplatast Tosilate (IPD®, Taiho Pharmaceutical Co., Japan) currently being used for the treatment of atopic disorders, has recently been tested in 7 patients with vitiligo. In 3 patients, repigmentation could be observed. In another 3, the disease had stabilized and in 2 of them also microsome test and thyroid test titer were reduced. No side effects were reported. It is suggested that the drug acts through its inhibitory effect on interleukine-4, which is an important cytokine in the stimulation of antibody production by B-cells\textsuperscript{320}. This study was however uncontrolled and the results have not yet been confirmed by other treatment centers.

Melagenine and infrared and/or UV radiation

Melagenine is a hydroalcoholic extract of the human placenta that is synthesized in Cuba\textsuperscript{321}. Topical melagenine in combination with infrared radiation or exposure to natural
sunlight have been reported to be effective for the treatment of vitiligo. However, this could not be confirmed by other investigators\textsuperscript{322}. There is not much known about the biochemistry, biologic activity and pharmacology of this drug. Melagenine may contain a lipoprotein that stimulates melanogenesis and melanocyte proliferation. To date, there seems to be a poor quality control in the production of this drug\textsuperscript{323}.

**Grafting of follicular melanocytes**

Repigmentation of leukotrichia in vitiligo has been achieved using epidermal blister grafting in combination with oral PUVA by Hann et al.\textsuperscript{324} and using single hair grafting technique by Na et al.\textsuperscript{325}. These observations suggest that epidermal melanocytes could migrate or transfer to the hair follicle. Direct evidence for such a mechanism has not yet been provided.

Because outer root sheaths (ORS) melanocytes constitute a natural reservoir for the repigmentation process in vitiligo, they may be useful for grafting purposes. Further studies are needed to investigate the therapeutic possibilities of such techniques in vitiligo.

In the past decade, there has been an outburst of new therapeutic modalities for vitiligo. This reflects the frustration of investigators and clinicians towards classical vitiligo therapies such as PUVA therapy. The list of new therapies as discussed above is far from complete. The results of studies that report on new vitiligo therapies should be interpreted with caution; most of the studies were uncontrolled and/or had included only a few patients. Some therapies are promising, but more studies are needed to establish the long-term effectiveness and safety.

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