bodies against these antigens (20–22). Moreover, the number of circulating MART-1-reactive T cells expressing CLA in patients with vitiligo correlated with the extent of depigmentation (18).

In perilesional skin, $CD8^+$ T cells, macrophages and to a lesser extent $CD4^+$ T cells were found (23,24). Infiltrating $CD8^+$ T cells expressed skin homing, cutaneous leukocyte-associated antigen (CLA) and T-cell activation markers CD25, perforin and granzyme B (25), and colocalized with disappearing melanocytes. Finally, perilesional melanocyte-reactive $CD8^+$ cytotoxic T cells were shown to be capable of actively killing melanocytes in autologous skin tissue (J.G. van den Boorn, D. Konijnenberg, T.A.M. Dellemijn, J.P.W. van der Veen, J.D. Bos, C.J.M. Melief, F.A. Vyth-Dreese and R.M. Luiten, unpublished data).

Taken together, the pathogenesis of vitiligo results from changes in biochemical processes in the skin that trigger autoimmunity, which is enhanced by genetic predisposition to autoimmunity.

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Commentary 6

Vitiligo is the most common depigmenting disorder which is determined by both genetic and environmental factors (1). During the last two decades, however, investigators have focused mainly on the genetics aspects of vitiligo rather than on the environmental side. For example, scholars have not only found more than 10 candidate genes for vitiligo (2–11), but also located several susceptibility genes to vitiligo on chromosomes one, four and six (8,12–15).

At the same time, the evidence base for environmental factors is weak despite the often heard expression that: 'vitiligo, as a complex disease, is affected by both genetic and environmental factors'. In our current post-genomic era, genetics and genomics research is perceived to be 'hot' and epidemiological research to environmental risk factors runs the risk to be undervalued. Especially in the context of complex diseases, it is our duty to investigate all aspects of causation and not only the 'sexy' ones.

Patients with vitiligo often assume that their disease is triggered by an environmental exposure such as sunlight, hair dye or paint (16). From anecdotal evidence (JBL) in clinical practice, we learned that trauma often seems to precede vitiligo as well. In many cases, the initial site of vitiligo is a wounded area.

Gauthier recently proposed the *melanocytorrhagy hypothesis* which may explain this trauma-induced vitiligo (17,18). Based on morphologic findings, his theory assumed melanocytorrhagy as the primary defect underlying melanocyte loss and integrated most of the possible triggering/precipitating/enhancing effects of other known factors, such as genetic, autoimmune, neural defections and impaired redox status (19–22).

Despite the well-known nature-nurture debate on the causation of many complex diseases, no paper as yet systemically studied or reviewed environmental risk factors of vitiligo. This is disappointing. Some potential environmental factors were collected in our recently conducted genetic epidemiological study on vitiligo using 3742 patients (1,23). Here, for discussion, we put forward an interesting but yet unpublished finding from this study on the relation between sunlight and vitiligo. We observed that exposure to sunlight might be negatively associated with vitiligo (OR 0.709, 95% CI: 0.453–1.111), especially for women (OR 0.506, 95% CI: 0.263–0.974). This finding is opposite to the experience described above. Today, however, no evidence is available that can prove or disprove the potential protective effect of sunlight on the incidence of vitiligo. It is well known that narrow-band UV-B can be used to treat vitiligo directly (24) and sunlight does accelerate repigmenting during the treatment by PUVA. Could sunlight, perhaps, even exert beneficial effects in vitiligo?

As the heritability of vitiligo is observed to be around 50% (1), environment should contribute largely to the development of vitiligo. As with many complex diseases, we believe that an interleaving net constructed by both genetic and environmental factors should be considered as a general model of vitiligo pathogenesis. Identifying those disease-modulatory environmental factors is both a formidable and important task for epidemiologists and dermatologists in the next decade.

We hope that this contribution will stimulate more research into the environmental determinants of vitiligo. As the genetic constitution of an individual cannot be changed, perhaps 1 day in-depth knowledge on environmental risk factors can prevent vitiligo in some individuals by changing the unfavourable environment.

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Commentary 7

Vitiligo is a common cutaneous disorder that affects between 1% and 2% of the population and can broadly be classified into generalized or localized varieties (1,2). Generalized vitiligo is characterized by lesions of de-pigmented skin which are often symmetrically placed and frequently affect the body orifices and acral areas (1,3). While the condition is not life threatening, it is associated with low self-esteem, depression and can be particularly distressing when mistaken for tuberculoid leprosy (4–6).

The aetiology of vitiligo is controversial and working hypotheses include a genetic predilection, abnormalities in biochemical/neural intermediates and autoimmunity [reviewed in Ref. (7)]. However, the majority of evidence supports the supposition that there is an underlying autoimmune disorder resulting in the targeted destruction of melanocytes and the subsequent characteristic formation of depigmented macules. Clinical data linking vitiligo with other autoimmune conditions (including diabetes, Addison's disease, lupus erythematosus and rheumatoid arthritis) supports the autoimmune hypothesis, and immuno-modulatory agents have been used to treat the condition (8). Vitiligo is accompanied by abnormalities in both the humoral and cellular immune compartments and high levels of circulating autoantibodies, predominantly of the IgG class, have been detected in the sera of patients (9,10). However, the role of anti-melanocyte antibodies in the pathogenesis of vitiligo remains unclear and it has been suggested that their presence may be secondary to cellular damage (10).

Vitiligo pathogenesis: CD4 T cells should move to centre stage

The identification of cytotoxic lymphocytes responsible for the initiation of the autoimmune process has been seen as a critical first step towards developing effective therapeutics. The use of MHC tetramer technology has allowed the isolation and characterization of $CD8^+$ T cells, from patients with vitiligo, which can mediate targeted melanocyte cell death (11,12). These same cytotoxic lymphocytes may be important for the treatment of malignant melanoma, as the same melanocyte-specific antigens which are autoimmune targets in vitiligo are expressed on melanoma cells and immune responses directed toward these antigens can eliminate cancerous cells (13,14). Patients with melanoma who are successfully treated with interleukin-2 often present with vitiligo (15). As $CD8^+$ cells are the principal cytotoxic T cell *in vivo*, there is a concerted effort to manipulate this cellular subset to improve prognosis in cutaneous disease. Immuniza-

