Report on the 19th IPCC Satellite Symposium on Vitiligo 23 Sept 2005, Reston, Virginia

This one-day symposium was sponsored by the International Federation of Pigment Cell Societies (IFPCS), and organised by Alain Taïeb and Mauro Picardo who are currently chairing the special interest group on Vitiligo of the IFPCS. Vince Hearing, the organizer of the 19th IPCC, was very kind to help the logistics of this satellite meeting.
The main objective of the meeting was to foster cooperation within the international community of clinicians and scientists present at the meeting around this common but poorly understood disease that causes much distress especially in dark-skinned communities. Patients' support organisations from all over the world had also been invited to attend and to speak. Maxine Whitton, from the UK vitiligo Society, who could not attend, sent a very thought-provoking paper to the organizers, which helped to shape the discussion on topics ranging from classification of vitiligo and its possible implications for treatment, nature of depigmentation, epidemiology, sunlight and UVB, to basic science and treatment.
The symposium programme took into consideration the IPCC main programme which had already covered a broad range of topics, with two plenary lectures, Raymond Boissy on contact depigmentation and Richard Spritz on the genetics of non-segmental vitiligo, as well as several oral communications and posters (**see list in Appendix 1**). It was decided to give some extra time for the discussion of posters from the main meeting corresponding to the focuses of the satellite sessions, after a summary presentation by the authors.

Session I: Definition of disease, assessment and outcome measures

Chairs: M Picardo and A Taïeb

1. Alain Taieb[1] (Bordeaux, France) presented the work done on this topic by the Vitiligo European Task force (VETF). Alain Taieb mentioned that he wanted to build on his previous fruitful collaborative work for atopic dermatitis, which, through the European Task Force on Atopic Dermatitis (ETFAD), has produced over the last 15 years a widely accepted scoring system (SCORAD), a standardisation of atopy patch tests, and position papers on this disease. His presentation gave a special emphasis on the assessment workshop held in Rome on January 16, 2005 (**IPCC Poster 051, PCR 18, suppl 1, p 68-9**). The VETF was created in 2003 during the ESPCR in Ghent organized by Jean Marie Naeyaert (**Fig 1**) to design tools for clinical research in vitiligo and promote collaborative studies. Two subsequent workshops were held in Paris in 2004 with the aim to design a common evaluation/scoring form which was tested at 11 European clinical centres on 180 patients included in a common database managed in Rome by the San Gallicano Group's statistican, Mario Pellicciotta.

Fig 1

[1] On behalf of VETF members: A Alomar (Barcelona), D Bennett (London), M Böhm (Münster), Y Gauthier (Bordeaux), D Gawkrodger (Sheffield), S Moretti (Florence), T Passeron (Nice), G Leone and M Picardo (Rome), M Olsson (Uppsala), G Orecchia (Pavia), K Ongenae, N van Geel, JM Naeyaert (Ghent), W Westerhof and JP Wietze van der Veen (Amsterdam),

The VETF has chosen to use the simplified **classification of vitiligo**, following Koga's 1977 paper distinguishing segmental and non-segmental forms of disease, but based more on pragmatic than on pathophysiological grounds. However the VETF data collected allows a more accurate classification if needed (including focal, mucosal, acrofacial, common generalised, universal and even more subgroups) since the topography of lesions is reported in the assessment form. The VETF **consensus definition** for **non-segmental vitiligo** is as follows: an acquired, chronic, pigmentation disorder, characterised by white patches, often symmetrical, usually increasing in size with time, and which are due to a substantial loss of functioning epidermal and /or hair follicle melanocytes. The counterpart of this consensus definition is a list of disorders to exclude, namely piebaldism and other monogenic hypomelanoses, including tuberous sclerosis; post inflammatory depigmentation, including mycosis fungoides; post infectious depigmentation such as that seen in pityriasis versicolor, leprosy; post traumatic leucoderma; melanoma-associated leucoderma; melasma; toxic and drug-induced depigmentation (topical and systemic). The Rome San Gallicano Dermatological Institute (SGDI) workshop was presented to the audience. Its objective was (1) to further test how practical is the VETF evaluation system (**Appendix 2**) which includes 3 main items related to extent, spreading, and staging, and (2) to assess inter-observer variations in scoring patients. 10 dermatologists from 9 European centres could examine 13 patients (8 NSV, 5 SV). For each patient a patch to be assessed was chosen by the organising SGDI team in order to reduce the duration of the session. The patient's opinion about the progression of the selected patch was recorded separately and did not influence the investigators. The dermatologists did not communicate during the session. 130 evaluations of the 3 scoring items were collected and analysed *vs* standardized colour and black and white UV photographs (prototype instrument, Deka, Florence, Italy). The workshop validated the clinical use of the assessment form proposed and showed an overall good concordance among panelists. It however raised several problems, e.g. staging since colour of the selected patch is not homogeneous especially in segmental vitiligo. Staging chosen by investigators reflected generally the worst stage. This poses problems when a few white hairs are present in association with skin repigmentation. A proposal was made for simplifying the staging system (stage 4 deleted). Another difficulty was related to the need to magnify the lesions to assess hairs, especially vellus hairs. Wood's lamp equipment for vitiligo assessment should include a magnifying lens. Analysis of spreading (progressive/stable/regressive) was the most difficult item in a blind (not patient influenced) test. Surprisingly, the investigator's opinion was right in the majority of cases if the patient's opinion was chosen as the gold standard. Overall, it was felt that this item should be graded more accurately using the patient's opinion.

Alain Taïeb summarized his most important points: (1) The SGDI workshop validated a simple clinical assessment system of vitiligo, which can be easily handled in clinical practice. (2) Proposals for simplification of the tested EVTF assessment system were made for the grading grid. (3) Scorer profiles underscore the need of training to decrease inter-observer variability. He delineated desirable further steps, namely (1) including staging and spreading in the initial assessment of patients, in order to build a global index, most important for therapeutic indications and prognosis, which could be understood as an equivalent of the TNM system for cancer; (2) further large scale tests are needed in clinical trials (to check reproducibility, and sensitivity), and refinements using automated devices should be encouraged for special purposes, as well as teaching tools, which could be posted on an internet site, such as the ESPCR website. (3) An international agreement for classifying, staging and scoring vitiligo could be set as a main objective of the IFPCS special interest group on Vitiligo.

2. **Ilt Hamzavi** (Detroit, USA) presented the work he published recently with his colleagues while at the University of British Columbia in Vancouver[2] which uses a quantitative parametric score, named the VASI score for Vitiligo Area Scoring Index, which is conceptually derived from the PASI score widely used for psoriasis. He made the point that many vitiligo treatments have typically been analysed using nominal binary scales in which the proportion of treated patients who either do or do not achieve a specified degree of repigmentation is reported and compared by nonparametric statistical approaches. The degree of repigmentation that defines success has often been set previously somewhat arbitrarily at 50% to 75% repigmentation based largely on the global impression of the overall response. Quantitative methods provide data that are generally more intuitive and meaningful to patients and physicians, while at the same time being more sensitive for detecting significant subtle treatment effects. In addition, a quantitative method for measuring vitiligo severity would allow more studies to be compared across a range of data sets. A simple quantitative technique could standardize vitiligo outcome measurements and allow more studies to be included in meta-analyses.

In VASI, the body is divided into 5 separate and mutually exclusive regions: hands, upper extremities (excluding hands), trunk, lower extremities (excluding the feet), and feet. The axillary and inguinal regions are included with the upper and lower extremities, respectively, while the buttocks are included with the lower extremities. The face and neck areas are not included in the overall evaluation. One hand unit, which encompasses the palm plus the volar surface of all the digits, is approximately 1% of the total body surface area and is used as a guide to estimate the baseline percentage of vitiligo involvement of each body region. Depigmentation within each area was estimated to the nearest of 1 of the following percentages: 0, 10%, 25%, 50%, 75%, 90%, or 100% (**Figure 2)**

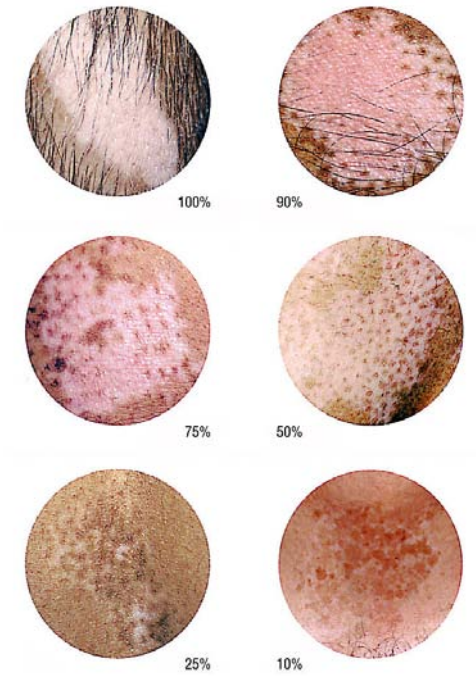


Figure 2: **%** depigmentation visual scale

For each body region, the VASI is determined by the product of the area of vitiligo in hand units (which was set at 1% per unit) and the extent of depigmentation within each hand unit–measured patch (possible values of 0, 10%, 25%, 50%, 75%, 90%, or 100%). The total body VASI is then

[2] Hamzavi I, Jain H, McLean D, Shapiro J, Zeng H, Lui H. Parametric modeling of narrowband UV-B phototherapy for vitiligo using a novel quantitative tool: the Vitiligo Area Scoring Index. Arch Dermatol. 2004 Jun;140(6):677-83.

calculated using the following formula by considering the contributions of all body regions (possible range, 0-100):

VASI = $\Sigma_{\text{(all body sites)}}$ (hand units) x (depigmentation)

Dr Hamzavi stressed that using quantitative scales can more easily capture sequential trends in response by time or treatment number. Although such data for vitiligo are currently unavailable, they are nevertheless important because at the present time patients with vitiligo are asked to commit to treatment for a year or more based largely on knowing only the probability of achieving a certain specific degree of repigmentation at the end of therapy without any actual data on the expected rate of response over time. The VASI provides a sensitive method for detecting treatment responses, as evidenced by the demonstration of a significant difference between NB–UV-B and control within 2 months of treatment. If the Archives' published study had used a nonparametric method to evaluate response and chosen the usual 75% repigmentation threshold as representing treatment success, the trial would have shown a non-significant result (P = .50 by the McNemar test) instead of the highly significant difference found using the VASI (P<.001). Also, the VASI provides information over a range of time points rather than an arbitrarily set end point. When compared, the correlation with the VASI was lower for patient assessment than for physician assessment but-was still statistically significant. The difference may be owing to a wider variation in what patients perceive to represent improvement. Dr Hamzavi said that it was important for other investigators to evaluate the validity of this technique, and he believes it is a quick and reliable tool, which can be applied to any setting and treatment.

3. Other papers of this session were presented by David Gawkrodger (Sheffield, UK) and A.J. Kanwar (Chandigarh, India).

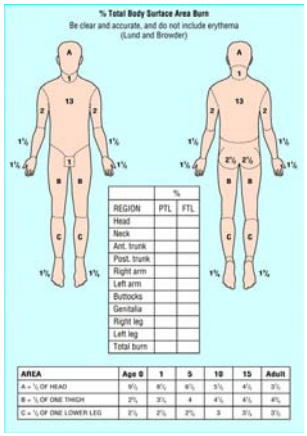
Dr Gawkrodger presented a classification of vitiligo according to clinical pattern and disease association, based on the prospective evaluation of 41 adult patients, stressing the importance of a careful clinical evaluation. He found a 18% family history of vitiligo, 34% of patients had autoimmune thyroid disease, and 33% a family history of endocrine autoimmune disease.

Dr Kanwar examined 212 patients with onset of vitiligo after 50 years of age. Associated endocrine autoimmune disorders were present in 21.4% and 15.9% had a family history of vitiligo. Segmental vitiligo is rare in this age group (5.4%).

Discussion:

Dr M Ramam (New Delhi, India), suggested using the Lund Browder chart to score extent, because its advantage over the "rule of nines" is that the denominator is smaller for many body areas. As pointed out during Dr Taïeb's presentation, the difficulty in assessing surface area involvement is greatest when the denominator is large as on the legs. He further suggested that studies reporting on the response to treatment in vitiligo mention how many patients have achieved complete (100%) repigmentation. He said that this information is usually pooled together with those who have more than 75% repigmentation. However, for patients and those treating vitiligo, the difference between 100% repigmentation and 90% repigmentation is great.

Fig 3: Figure of the Lung and Browder chart reproduced from Hettiaratchy, S. et al. BMJ 2004;329:101-103



Another point was made concerning Dr Hamzavi's presentation by Dr Taïeb, indicating that multiplying extent by lesional score as in PASI is a potential source of error and increased variability between investigators, which has been avoided in other scales such as SCORAD which is an additive index combining extent, intensity and subjective signs.

Among questions taken from **Maxine Whitton's** list:
Prevalence of vitiligo: experts in the audience agreed on a population based prevalence around 1% or less, but this figure might be increased in particular ethnic backgrounds.
Location of disease and resistance to treatment: **Dr Nordlund** (Cincinnati, USA) replied to the question of differential responses to treatment according to location of disease, by emphasizing the role of the reservoir of melanocytes which is found in hair follicles and absent on mucosal and glabrous skin such as the hands, and the role of precipitating/ environmental factors, especially trauma (Koebner's phenomenon).
Segmental and non segmental vitiligo, a different disease or just a type of vitiligo? The hypothesis of a mosaicism for a major predisposing gene especially in stemness genes was already proposed but not yet investigated[3], and there are cases associating NSV and SV which point to applications of the concept of type II mosaicism[4] in multigenic diseases, corresponding in the segmental lesion to a possible double dosing of the major predisposing gene, and a more recalcitrant form of vitiligo in the corresponding area (Dr Nordlund, Dr Taïeb).

Session II: Evidence-based therapy and future trends

Chairs: W Westerhof (Amsterdam, NL), J Nordlund (Cincinnati, USA), Y Gauthier (Bordeaux, France)

There were four invited presentations, made by Dr Davinder Parsad (Chandigarh, India) on medical treatments, Dr Mats Olsson (Uppsala, Sweden), on surgical treatments, Dr Pearl Grimes (Los Angeles, USA), on combined therapies, and Dr H Lim who could not join the meeting was replaced by Dr Hamzavi (Detroit, USA) on phototherapies.

[3] Taieb A.Intrinsic and extrinsic pathomechanisms in vitiligo. Pigment Cell Res. 2000;13 Suppl 8:41-7.
[4] Poblete-Gutierrez P, Wiederholt T, Konig A, Jugert FK, Marquardt Y, Rubben A, Merk HF, Happle R, Frank J. Allelic loss underlies type 2 segmental Hailey-Hailey disease, providing molecular confirmation of a novel genetic concept. J Clin Invest. 2004 Nov;114(10):1467-74.

A Cochrane systematic review of interventions for vitiligo is currently in press as mentioned in her presentation sent to the organizers by Maxine Whitton who worked on this review with Dr Urba Gonzales from Barcelona and Darren Ashcroft, statistician from Manchester. This review could assess 19 randomised controlled trials (RCT) with an overall poor methodology, since the method of randomisation was rarely described, and that only 9 studies were double blinded. There was overall weak evidence for the effectiveness of interventions for vitiligo, including alternative and experimental. All measures of outcome related to re-pigmentation, while none considered depigmentation, cosmetic camouflage, or psychological interventions. No pooling was possible since no two trials compared the same intervention. The design was different between studies (left/right comparison, individual patches assessed, or comparisons between groups). Interestingly, placebo effects seemed limited, since in many trials none of the patients who received placebo improved. The relative risks and confidence intervals were large, inducing a high level of uncertainty. Important observations were made in this review: 1. There are large variations in methods for scoring repigmentation 2. There are no reliable data on patient-centred outcomes or quality of life measures. 3. There is a lack of any reliable measure of outcome. 4. Trials are too short to assess effectiveness or adverse effects. 5. Few studies are done in children. 6. Age, duration, type (segmental responds best to surgery), and choice of site (face versus limb extremities) could affect outcome. 7. Lack of consensus about a cause leads to a multiplicity of treatments. 8. No clear clinical guidance emerged from the review, but some implications for research priorities: there is a need for more basic research on causes; agreement on classification and standardised measurement of outcome; translational research from scientific discovery to RCT, and more research into psychological interventions. Patient-centred outcomes would improve study designs.

Most of these difficulties outlined in the review were considered in the invited oral presentations given at the meeting. Dr Parsad emphasised also the various effects of treatments on repigmentation patterns and stability [5]. Diffuse repigmentation is the least stable. Psoralens predominantly exhibit a perifollicular pattern of repigmentation and steroids (topical/systemic), a diffuse type. The speed of repigmentation is much faster when initial repigmentation is of the diffuse type as compared with follicular repigmentation. Marginal and perifollicular repigmentation are more stable than the diffuse type of repigmentation. Dr Olsson made remarks on the selection of patients for surgical procedures and specific transplantation methods[6]. Dr Hemzavi indicated that the evidence for effectiveness of UVBTL01 was the best following the pioneering work of Dr Westerhof in Amsterdam, both for adults and children[7]. Targeted phototherapy using excimer 308 xenon-chloride laser or monochromatic excimer light (MEL) are promising for some locations and limited disease. Combination with tacrolimus is synergistic. Dr Grimes emphasised the role of calcineurin inhibitors (tacrolimus, pimecrolimus), which are immunosuppressive, in combination with surgical and phototherapy interventions. A summary of the current approaches to treatment can be found in the following Table.

[5] Parsad D, Pandhi R, Dogra S, Kumar B. Clinical study of repigmentation patterns with different treatment modalities and their correlation with speed and stability of repigmentation in 352 vitiliginous patches. J Am Acad Dermatol. 2004;50:63-7.

[6] Olsson MJ, Juhlin L.Long-term follow-up of leucoderma patients treated with transplants of autologous cultured melanocytes, ultrathin epidermal sheets and basal cell layer suspension. Br J Dermatol. 2002;147:893-904.

[7] Westerhof W, Nieuweboer-Krobotova L. Treatment of vitiligo with UV-B radiation vs topical psoralen plus UV-A. Arch Dermatol. 1997;133:1525-8. ; Njoo MD, Bos JD, Westerhof W.Treatment of generalized vitiligo in children with narrow-band (TL-01) UVB radiation therapy. J Am Acad Dermatol. 2000;42(2 Pt 1):245-53.

Type of Vitiligo	Usual management
Segmental (includes focal and mucosal)	**First line**: Avoidance of triggering factors, local therapies (corticosteroids, calcineurin inhibitors). **Second line:** Localized UVB therapy, especially Excimer lamp or laser. **Third line**: Consider surgical techniques if repigmentation cosmetically unsatisfactory.
Non segmental (including acrofacial)	**First line**: Stabilization with UVB TL01 therapy, at least 4 months. Combination with systemic/ topical therapies, including reinforcement with localized UVB therapy, possible. **Second line:** Consider surgical techniques in non responding areas especially with high cosmetic impact. However, Koebner phenomenon limits the persistence of grafts. Relative contraindication in areas such as dorsum of hands.

TABLE 1. General outline of management for vitiligo (adapted from Taieb, 2005, in press)

Five short presentations were given on tissue culture techniques (S Mac Neil, Sheffield, UK, and DN Hu, New York, USA), physical treatments namely Excimer Laser (A Overbeck, Madrid, Spain) and low energy helium-neon laser (CS Wu, Taipei, Taiwan), and adjuvant growth factor therapy (A. Ramaiah, Hyperabad, India). Dr Mac Neil presented the data (**PP053, OP 120**) which are promising in terms of delivering to distant centres melanocytes grown on a chemically defined surface (acid and amine plasma polymers) which have been transferred successfully to an in vitro model of human dermis. Dr Dan-Ning Hu showed an update of a study using pure autologous melanocytes in 150 vitiligo patients Taiwan[8], with better results in segmental and stable generalised cases. Dr Wu (PP046), working on the assumption that SV results from the dysfunction of sympathetic nerves in the affected areas, expanded his earlier observations[9] in an updated series of 40 patients, indicating that low energy helium-neon laser 632.8nm can repair nerve injury and improve SV. Dr Overbeck shared his experience with the excimer laser and showed encouraging results with a combined blister graft plus excimer laser technique. Dr Ramaiah (**OP 118**) indicated that his bFGF peptide lotion which is marketed in India can be used in combinatorial protocols.

Discussion:

Indications for surgical treatment: Several panellists warned against such therapies in patients who are not clearly stabilized. Surgery on hands needs immobilization which is not easy to obtain in practice.

Non melanoma and melanoma skin cancer and UV exposure in vitiligo patients. There is no demonstrated increased risk from UV in vitiliginous skin (and the contrary is suggested based on anecdotal reports in tropical countries) and UVBTL01 treatment is considered as a safe first-line

[8] Chen YF, Yang PY, Hu DN, Kuo FS, Hung CS, Hung CM. Treatment of vitiligo by transplantation of cultured pure melanocyte suspension: analysis of 120 cases. J Am Acad Dermatol. 2004;51:68-74.

[9] Yu HS, Wu CS, Yu CL, Kao YH, Chiou MH. Helium-neon laser irradiation stimulates migration and proliferation in melanocytes and induces repigmentation in segmental-type vitiligo.J Invest Dermatol. 2003;120:56-64.

therapy in vitiligo. There is no need to avoid natural sunlight, since UVB boosts melanocyte division and migration. UVA may act indirectly on the melanocyte environment, through growth factor production by epidermal and dermal cells, promoting melanocyte survival and pigmentation. A moderate suberythemal exposure (that is, less exposure than leads to sunburn) is advised to enhance repigmentation, followed by sun protection if further exposure cannot be avoided (summary of various panellists' answers). It is often assumed that skin is protected against sunburn predominantly by melanin. However, Dr Westerhof mentioned a difference in burning capacity of white patches between vitiligo individuals with different skin types. With UVB 311 nm lamps, he irradiated both lesional and non-lesional skin with increasing doses in 33 patients with vitiligo, divided into 5 groups according to skin type (II-VI). Twenty-four hours later he assessed the minimal erythemal dose and found a correlation between skin type and UV sensitivity in both lesional skin and normal skin. He suggests that there must be a protection mechanism, other than that offered by melanin pigmentation. Antioxidant status may play a role in this phenomenon[10].
UV treatments in children: The benefit/risk ratio is frequently evaluated with a strong negative bias in children because the potential side effects of treatments are overemphasized. However, the benefit of an early stabilizing treatment is currently considered more important than the risk of UV irradiation. The limiting factor is the practical management of UVBTL01 therapy in a child, which is generally possible only around the age of 6-7 or older.[11]

Session III: New directions for research (Interface between clinical and basic research)

Chairs: C Goding (Oxted, UK), A Taïeb (Bordeaux, France)
Panelists: L Larue (Orsay, France), D Bennett (London, UK), P Das (Amsterdam, NL), R Spritz (Denver, USA)

Non immune and immune pathomechanisms were respectively introduced by Mauro Picardo (Rome, Italy) and Caroline LePoole (Chicago, USA).

Dr Picardo reviewed primary cellular defects and alterations of the melanocyte microenvironment that can lead to the disappearance of functional melanocytes, and considered auto-immune phenomena as secondary. He made the point that vitiligo is probably not a single disease and that it may correspond to multiple causes. He examined neural, metabolic, genetic, redox and adhesion dependent (melanocytorrhagic[12]) mechanisms. Melanogenic and extra-melanogenic metabolism, including for the latter catecholamines, calcium, antioxidant, and pterins, have all been shown to be altered to some extent in vivo or in vitro. A clear genetic basis for these alterations is not yet at hand. He made the hypothesis that altered gene expression could affect the amount or the correct folding of proteins involved in the synthesis of melanin or in the detoxifying process, with subsequent increased melanocyte vulnerability. He emphasized the current evidence for a compromised intracellular redox status due to both impaired antioxidant defence and increased free radical production. The detachment of melanocytes could be the net effect of convergent pathways altering melanocyte survival and give rise to secondary autoimmune responses.

[10] Caron-Schreinemachers AL, Kingswijk MM, Bos JD, Westerhof W. UVB 311 nm tolerance of vitiligo skin increases with skin phototype. Acta Derm Venereol. 2005;85:24-6.
[11] Atherton DJ, Cohen BL, Knobler E, Garzon M, Morelli JG, Tay YK, Weston WL, Taieb A, Morison WL, Rasmussen JE. Phototherapy for children. Pediatr Dermatol. 1996;13:415-26.
[12] Gauthier Y, Cario Andre M, Taieb A. A critical appraisal of vitiligo etiologic theories. Is melanocyte loss a melanocytorrhagy? Pigment Cell Res. 2003;16:322-32.

Dr LePoole stated that in vitiligo depigmentation is accompanied by T cell influx to the skin in the vast majority of patients, in an entity she designated as "auto-immune vitiligo". A minority of such infiltrating T cells are type 1 proinflammatory cytokine-secreting cells reactive with melanocyte-specific antigen. Melanoma research has shown that differentiation antigens, also expressed by normal melanocytes, can be immunogenic when expressed in the melanosomal compartment of the cell. Similar reactivity to melanosomal antigens is apparent for T cells infiltrating vitiligo skin. Stress may be a precipitating factor of the immune response inadequately modulated by regulatory T cells. T cells are recruited to the skin as a function of dendritic cell activation and dendritic cells are likely activated at sites of epidermal trauma as a consequence of stress proteins such as HSP that spill over into the microenvironment. Stress proteins chaperoning antigens representative of the cells from which they were derived are then processed by dendritic cells and contribute to their activation. Activated dendritic cells not only migrate to draining lymph nodes to recruit T cells but may execute cytotoxic effector functions as well. The contribution of the effector functions to actual depigmentation of the skin remains to be investigated.

A first debate was launched based on these two reviews and on the list of questions from the UK Vitiligo Society summarized by Maxine Whitton.

Colin Goding speculated on a common stress signalling pathway hypothesis which may reconcile immune and non-immune pathomechanisms, acting on both keratinocytes which provide survival and growth promoting factors for melanocytes, and of course melanocytes, as well as on various dermal cells which can influence melanocyte behaviour. Another hypothesis concerns alterations in stem cells that could also be influenced by stressor factors. He also underlined the role of the transcription factor MITF in the loss of melanocytes and in depigmentation. The relevance of this mechanism is supported by *in vivo* (mouse with *vit* gene deletion) and *in vitro* studies. The mitogen-activated kinase (MAPK) p38 has been shown to transduce a variety of stress stimuli including UV, mechanical and hormonal stress into cellular responses by phospho-relay cascades, which are possible research targets. One possibility raised is that melanocytes from vitiligo patients are intrinsically more sensitive to stress signalling via the p38 pathway.

In conclusion of this debate, Colin Goding summarized his views as follows: vitiligo appears to be a complex disease in which melanocytes are intrinsically stress sensitive, leading most likely to melanocyte death in response to various kinds of stress - mechanical, viral, even emotional. This would then lead to vitiligo only in those patients who also have genetic predisposition to an auto-immune reaction against melanocyte antigens.

Further questions from **Maxine Whitton** were addressed:

<u>Is there an agreement on the nature of pigment loss?</u> Are all the melanocytes in vitiliginous skin dead, or do some survive in the white patches, which can be stimulated to divide and multiply? This question refers to the staging of the disease and has important therapeutic consequences. However, the panellists present were not enthusiastic to answer it, because there are more opinions than facts on this matter. Repigmentation can occur from hair follicles and sometimes focally on glabrous skin such as lips – so surely most would agree that sometimes melanocytes or their precursors are still present within the patches in this case. We just don't know if they <u>always</u> are. Further research is obviously needed.

<u>Why does vitiligo appears on particular parts of the body?</u> What is different in those parts of the skin or underlying tissues that predisposes one part to manifest depigmentation and not another?

The panellists agreed upon the role of environmental/triggering factors especially trauma causing Koebner's phenomenon, but there are probably other unknown factors. Another point was made by Dr Lionel Larue (Orsay, France) who speculated about the role of melanocyte migration, which makes it take longer for the precursor cells to reach the extremities, so that fewer cells arrive in these areas. This may affect the susceptibility of melanocytes in acral locations. Prof Bennett commented that there was also speculation on a role for neurotransmitters, since some of the susceptible areas (e.g. around the eyes and mouth and the fingers) have a rich nerve supply.

Some people report itching in their vitiligo patches, often it is the precursor to a new white spot. For others the white patches are more sensitive to products such as soap and shampoo. If itching is an inflammatory response then all people with vitiligo should experience it (cf eczema, acne).
Has any research been done on itching in vitiligo?
Dr Taieb replied that so-called "inflammatory vitiligo" is a known but rare event and that pruritus is rarely mentioned spontaneously by patients visiting our clinics. This point was agreed upon by other clinical experts. Pruritus would be indeed a good argument for the autoimmune or auto-inflammatory theory of vitiligo. However, it appears important to obtain this information more systematically when taking the patient's history and even to use a pruritus scale in this disease. The VETF should include this item in the updated version of its vitiligo evaluation form.

Five short presentations were discussed in this session.
Dr Thomas Tüting (Bonn, Germany) presented a mouse model using C57BL/6 mice which indicates that CD4 T cell help and local inflammation are required to circumvent peripheral CD8 tolerance against melanocytic antigens. Using two different genetic methods for the induction of cellular immunity in vivo, gene gun bombardment of the skin and injection of recombinant adenovirus, his group has shown that peripheral tolerance of CD8+ T cells recognizing a single TRP2-derived H2-Kb-binding peptide is regulated in two steps. In the induction phase, stimulation and expansion of TRP2-specific CD8+ T cells in vivo depend on CD4+ T cell help. In the effector phase, autoimmune destruction of melanocytes in the skin depends on local inflammation. He suggest that accidental stimulation of CD8+ CTL recognizing major histocompatibility complex class I-binding peptides derived from melanocytic proteins in the context of an inflammatory skin disease may play an important role in the pathophysiology of vitiligo[13].
This paper raises an issue in line with one of the above questions, and would suggest a more thorough look at inflammatory premises of vitiligo which are so far not clear in most patients.

Dr Silvia Moretti (Florence, Italy), pursuing her previous work on done using immunohistochemistry of cytokine expression[14] described modifications in cytokine transcripts for ET1, SCF , GM-CSF, bFGF and TNF α in 12 patients with active NS vitiligo. ET1 and SCF were more expressed in perilesional than lesional skin, whereas GM-CSF and bFGF were more present in lesional than perilesional skin. TNFα, which has an inhibiting effect on melanocyte growth and differentiation, was highly expressed in both perilesional and lesional skin, but not detectable in normal control skin. Similar data for TNFα transcripts have been reported by Dr Grimes and colleagues[15]. During the discussion Dr Taïeb mentioned that if this finding is relevant, it was surprising that in the large number of patients treated with anti-TNF agents, no

[13] Steitz J, Bruck J, Lenz J, Buchs S, Tuting T. Peripheral CD8+ T cell tolerance against melanocytic self-antigens in the skin is regulated in two steps by CD4+ T cells and local inflammation: implications for the pathophysiology of vitiligo. J Invest Dermatol. 2005;124:144-50.
[14] Moretti S, Spallanzani A, Amato L, Hautmann G, Gallerani I, Fabiani M, Fabbri P. New insights into the pathogenesis of vitiligo: imbalance of epidermal cytokines at sites of lesions. Pigment Cell Res. 2002;15:87-92.
[15] Grimes PE, Morris R, Avaniss-Aghajani E, Soriano T, Meraz M, Metzger A. Topical tacrolimus therapy for vitiligo: therapeutic responses and skin messenger RNA expression of proinflammatory cytokines. J Am Acad Dermatol. 2004;51:52-61.

cure of vitiligo has been so far mentioned. One case of infliximab related vitiligo has even been published[16]. Dr Grimes mentioned that a study of anti-TNFα in vitiligo is under consideration at her institution.

Dr Paola Grammatico (Rome, Italy) took the candidate gene approach for NS vitiligo. She looked at CDKN2C, a tumor suppressor gene located in the AIS1 region recognized as a vitiligo susceptibility locus, at the microphthlalmia (MITF) gene which encodes a transcription factor important for melanocyte survival, and at the angiotensin converting gene (ACE) I/D polymorphisms recently reported in the Korean population in vitiligo patients. The results were negative when using Italian control samples. Dr Richard Spritz commented that candidate gene approaches should not be performed in multigenic disease given their very low yield of positive results. He has developed linkage studies that have been more fruitful.
However, Dr Taïeb pointed out that other complex diseases benefited from the candidate gene approach, when a monogenic disorder is highly associated with the considered phenotype, quoting the example of Netherton syndrome and atopic dermatitis[17].
Dr Muriel Cario-André (Bordeaux, France) summarized the prize winning IPCC poster (**PP 050**) which demonstrates a strong dermal influence on human epidermal pigmentation. Using epidermal reconstructs seeded on various types of dermis, in vitro and in vivo with xenografts on tolerant Swiss nu/nu mice, she showed that dermal fibroblast density/activity influences melanocyte migration and proliferation and possibly melanin distribution and degradation. How this applies to vitiligo and other skin disorders remains elusive but the findings suggest consideration of the dermal influence on the epidermal melanin unit as more important than previously envisaged.

Session IV: Burden of disease/Interaction with patients' support groups

Chair: Alida de Pase (ASNPV, Italy)
Alida de Pase has reported on this Satellite in a separate paper.
The interaction of patients' support groups with the medical and scientific community has already been fruitful as communicated by Richard Spritz at the IPCC, since major predisposing genes have been detected in the families contacted in the UK and North America by patient support groups. It was also important to have the personal account of the patients and they deputized brilliant speakers at the satellite meeting. Randy Salter from Vitiligo Support International reported on his personal experience, and how difficult it was in general to find doctors with an interest in vitiligo patients. A dePase also made a practical point during the meeting concerning paediatric patients, who should be seen in separate clinics because of losing all hope when mixed up with affected adults in the same waiting room. The AVRF (American Vitiligo Research Foundation) deputized Roxanne Knight and Marilyn Giordano who presented slides of severely affected children, bringing home to the audience the message of how urgent it was for the medical/scientific community to address the problem of vitiligo.

[16] Ramirez-Hernandez M, Marras C, Martinez-Escribano JA.Infliximab-induced vitiligo. Dermatology. 2005;210:79-80.
[17] Walley AJ, Chavanas S, Moffatt MF, Esnouf RM, Ubhi B, Lawrence R, Wong K, Abecasis GR, Jones EY, Harper JI, Hovnanian A, Cookson WO. Gene polymorphism in Netherton and common atopic disease. Nat Genet. 2001;29:175-8.

Conclusions

Mauro Picardo and Alain Taieb expressed their thanks to all the speakers and participants and delineated some future steps. The Special Interest Group on Vitiligo of the IFPCS should have a mailing list to communicate more easily on the internet, and receive messages concerning future initiatives. A specific website would be helpful. A vitiligo meeting will be held at the next ESPCR meeting in Barcelona organized by Luis Montoliu (24-27 Sept 2006) and at the next IPCC in Sapporo, Japan, May 7-12, 2008. Exchanges should be improved to promote an international agreement on such basic issues as assessment tools and outcome measures in clinical trials. Fostering exchanges between the clinical and scientific communities around vitiligo will be a priority and research projects could be set up based on some ideas debated at this Symposium. Fund raising for research is another important issue and the help of patient support groups is expected.

APPENDIX I: List of IPCC papers and posters related to vitiligo research

OP 2, 25, 35, 38, 74-77, 116, 117, 119-124
KL 5
PL 11-12
PP 33B, 33C, 36, 46, 47, 49-54, 56, 60A, 60C, 65

APPENDIX II: VETF assessment form