Summary of papers presented at the VETF Meeting in Honor of Yvon Gauthier, Bordeaux, 1st March 2008

Vitiligo: The Koebner phenomenon revisited and other topics

YVON GAUTHIER AND THE KOEBNER PHENOMENON

Alain Taïeb (Bordeaux)

Heinrich Köbner (1838-1904) was the founder of the dermatology clinic in Breslau (Germany, now Wroclaw, Poland) which was later led by the famous Neisser and Jadassohn. He described his eponymic phenomenon in 1872 in a case of psoriasis. This phenomenon was recognized by his contemporaries such as Kaposi and Darier *« les frottements continus ou les pressions répétées semblent lui servir de cause provocatrice ou d'appel et il n'est pas exceptionnel de voir chez les porteurs de bandages herniaires, un vitiligo débutant par les régions où s'applique la pelote ou la plaque dorsale »* Article VITILIGO by Jean Darier, in: La pratique dermatologique, 1900, T IV, p 849. Yvon Gauthier has developed in the 1990s a registry for mechanical trauma in vitiligo, urging that prevention matters (1). He has shown melanocyte detachment after standardized skin friction in non lesional skin of patients with NSV (2) and developed a new theory: the « melanocytorrhagy» (3). The rest of the presentation was focused on the micro-inflammatory theory of vitiligo as a possible missing link to explain the « melanocytorrhagy » (4). Arguments for suspecting a role of micro-inflammation as a destabilizing agent for melanocytes in common NSV vitiligo are the following : 1) the presence of microinfammatory foci at borders of depigmented lesions 2) Inactive pro IL1 present in stratum corneum 3) Koebner phenomenon: possibly related to low-key activation of epidermal reservoir of IL1 beta.
The Koebner phenomenon has had a great influence in the teaching at Bordeaux department of dermatology under Yvon Gauthier.

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THE KOEBNER PHENOMENON AND *IN VITRO* SUSCEPTIBILITY OF MELANOCYTES TO PHYSICAL AND CHEMICAL STIMULI.

M Picardo and ML Dell'Anna (Rome)

The Koebner phenomenon has been considered as a specific answer to non-specific stimuli, possibly accounting for melanocyte damage. The biological significance of this phenomenon was the basis of the presentation supported by in vitro data focusing on increased melanocyte sensitivity to external stimuli; alteration of adhesion processes; distruption of cell comunication; alteration of cell membrane function.

References :

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3: Dell'Anna ML, Ottaviani M, Albanesi V, Vidolin AP, Leone G, Ferraro C, Cossarizza A, Rossi L, Picardo M. Membrane lipid alterations as a possible basis for melanocyte degeneration in vitiligo. J Invest Dermatol. 2007 ;127:1226-33.

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6. Kroll TM, Bommiasamy H, Boissy RE, Hernandez C, Nickoloff BJ, Mestril R, Caroline Le Poole I.. 4-Tertiary butyl phenol exposure sensitizes human melanocytes to dendritic cell-mediated killing: relevance to vitiligo. J Invest Dermatol. 2005;124:798-806.

OCCUPATIONAL VITILIGO: BETWEEN KOEBNERIZATION AND ELICITATION.

JP W Van der Veen (Netherlands Inst for Pigment Disorders, Amsterdam)

In occupational vitiligo, melanocytoxic agents induce leucoderma, sometimes progressing into vitiligo. Occupational vitiligo may be a model for the pathogenesis of generalized vitiligo, since induced by a specific exogenous trigger as an experiment of nature.
The paper reported the prevalence of occupational Vitiligo in patients referred to the Netherlands Institute for Pigment Disorders during 2003-2007 based on the records of 1264 vitiligo patients. Evidence for chemically-induced vitiligo was found in 3 patients (0,2%). In 2 patients occupational vitiligo was diagnosed. One of these patients mentioned several colleagues who had the same problems. None of them sought medical advise or stopped the exposure.

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THE KOEBNER PHENOMENON AND OTHER SELECTION CRITERIA IN SURGICAL THERAPIES FOR VITILIGO

Nanny van Geel, MD, PhD

Department of Dermatology
University Hospital of Ghent
De Pintelaan 185, 9000 Ghent
Belgium
Tel: +32 9 332 6828
Fax: +32 9 240 49 96
Nanny.vangeel@Ugent.be

When considering surgical treatment in vitiligo, several selection criteria are of importance. The currently used parameters used in the vitiligo clinic of Ghent are: vitiligo type, total disease extension, resistance to non-surgical therapy, disease stability and age of the patients (Figure 1).
Disease stability has been considered to be the most important criterion in the selection. However, until now no consensus exists regarding the clinical evaluation of disease activity. According to the literature, the majority of authors classified vitiligo as being stable when further progression of lesions or development of new lesions were absent in the past year [1].

Clinical observation of lesions over time and evaluation of the Koebner phenomenon might be helpful in estimating disease stability. Others colleagues prefer to use a minigrafting test, although discussion exists about its usefulness[2]. Many investigators observed already that the presence of the Koebner phenomenon negatively influences surgical treatment results. This was clearly demonstrated in our double blind placebo controlled study of autologous non-cultured epidermal cell transplantation[3]. We demonstrated in this study as well that pre-treatment screening is a valuable tool to select patients, although it has limitations.
Regarding disease activity and the Koebner phenomenon, many uncertainties and discrepancies exist in the observations that have been described in the literature. For example, a Koebnerization at the donor site has been seen in combination with a stable vitiligo and even with a repigmentation of the surgically treated recipient area [4]. Besides, as in disease activity, a consensus regarding the definition of the Koebner phenomenon is still missing. As it is a dynamic process, this consensus should take the following items into account:

- What is the cut off point in time when using the patient's history to evaluate the Koebner phenomenon?
- Which depth of trauma could induce the Koebner phenomenon? Superficial Koebnerization (epidermal) or deeper (epidermal-dermal) Koebnerization?
- Is it a 'localized' or a 'generalized' phenomenon?
- What is the value of a "temporary" Koebner phenomenon?

Summarizing the literature we can state that there is no golden rule yet for successful surgical treatment as too many questions remain to be answered. The disagreement among dermatologists about definitions and inclusion criteria for surgical treatment will therefore still continue. This problem can probably be solved in the future if we could combine the clinical signs with an easy and reliable cellular analysis on blood or skin samples in daily practice. However, as vitiligo is a dynamic process, will we ever be able to determine the activity status or the future activity status correctly? So the ongoing research in this field seems to be very important. As long as a simple test is not available we have to use the present tools and should approach every person individually.

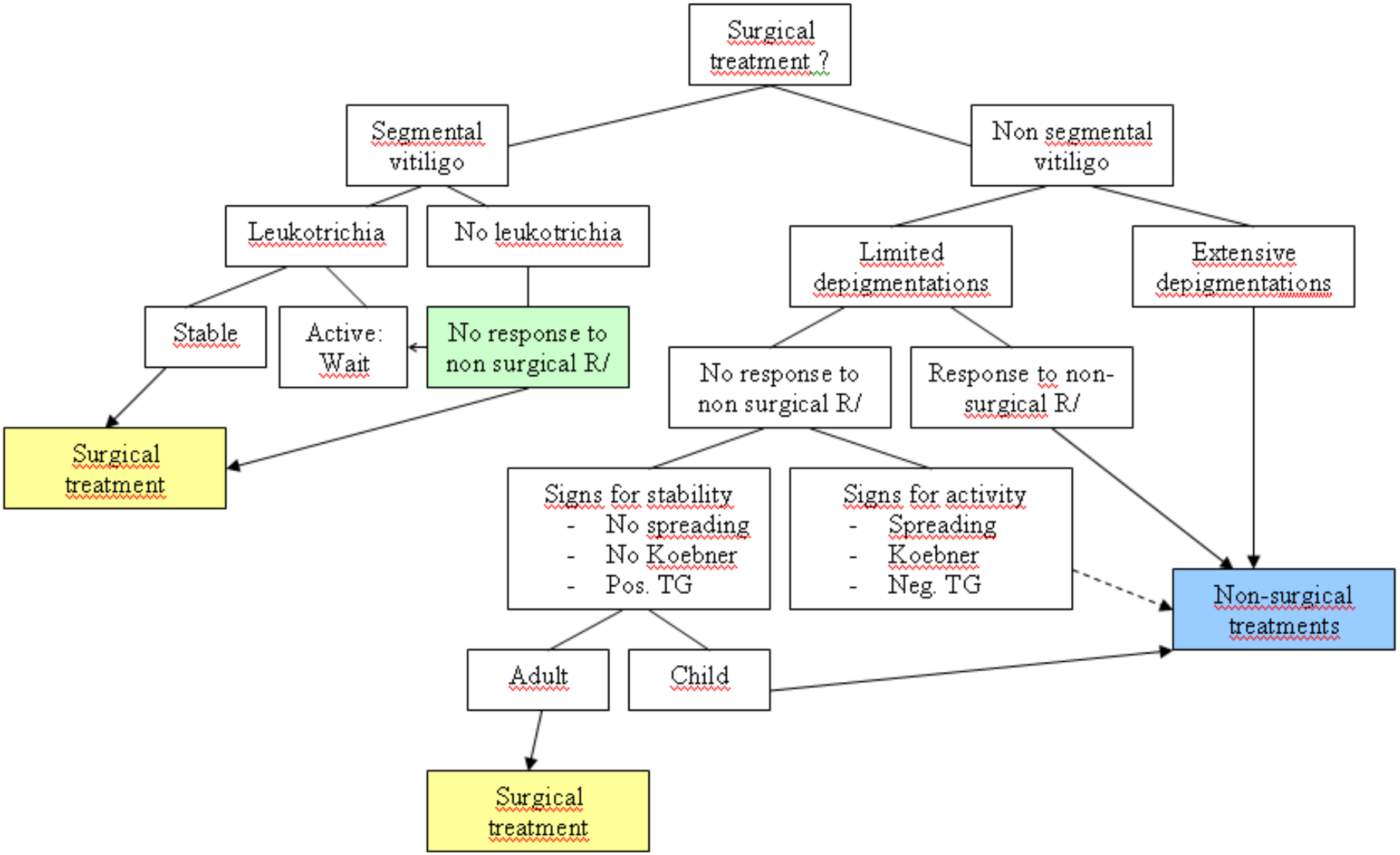

Figure 1: Flow chart including selection criteria used in University Hospital of Ghent (Belgium)

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2. Falabella R, Arrunategui A, Barona MI, Alzate A. The minigrafting test for vitiligo: detection of stable lesions for melanocyte transplantation. J Am Acad Dermatol 1995; 32(2 Pt 1):228-32.
3. van Geel N, Ongenae K, De Mil M, et al. Double-blind placebo-controlled study of autologous transplanted epidermal cell suspensions for repigmenting vitiligo. Arch Dermatol 2004; 140(10):1203-8.
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Alida de Pase (Milan): About "Turning White: a memoir of change" by Lee Thomas and news from patient's support associations

This short report focused on the coming out of a black TV journalist and its impact on the US public for the recognition of vitiligo as a disease with a high social and psychological burden.

TRANSCRIPTIONAL PROFILE OF MELANOCYTES FROM VITILIGO PATIENTS

Mats Olsson (Uppsala)

Vitiligo is a complex, polygenic disorder characterized by patchy loss of skin pigmentation due to abnormal melanocyte function. Both genetic and environmental etiological factors have been proposed for vitiligo and lack of molecular markers renders difficulties to predict development and progression of the disease. Identification of dysregulated genes has the potential to unravel biological pathways involved in vitiligo pathogenesis, facilitating discovery of potential biomarkers and novel therapeutic approaches. In this study, we characterized the transcriptional profile of melanocytes from vitiligo patients. Oligonucleotide microarrays containing approximately 16 000 unique genes were used to analyse mRNA expression in melanocytes from vitiligo patients and age-matched healthy controls. In total, 859 genes were identified as differentially expressed. A substantial number of these genes were involved in (i) melanocyte development, (ii) intracellular processing and trafficking of tyrosinase gene family proteins, (iii) packing and transportation of melanosomes, (iv) cell adhesion and (v) antigen processing and presentation. In conclusion, our results show a significantly different transcription profile in melanocytes from vitiligo patients compared with controls. Several genes of potential importance for the pathogenesis and development of vitiligo were identified. Our data indicate that autoimmunity involving melanocytes may be a secondary event in vitiligo patients caused by abnormal melanocyte function.

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Strömberg S, Björklund MG, Asplund A, Rimini R, Lundeberg J, Nilsson P, Pontén F, Olsson MJ.Transcriptional profiling of melanocytes from patients with vitiligo vulgaris. Pigment Cell Melanoma Res. 2008;21:162-71.

IS IT USEFUL TO COMBINE TOPICAL TREATMENTS WITH NARROWBAND UVB FOR VITILIGO?

Adrian Tanew (Vienna)

The paper reviewied first the effects of single therapy with emphasis on narrowband-UVB phototherapy, looked at the addition of vitamin D analogues, calcineurin inhibitors, pseudocatalase, catalase + superoxide dismutase, corticosteroids. For the latter, evidence is lacking. For vitamin D analogues and antioxidants, the evidence is scarce to absent. For tacrolimus, there is evidence for a faster and greater response when combined with the excimer laser and insufficient data regarding the combination with narrow-band UVB. In conclusion, if synergistic effect have been shown in several studies with acceleration of treatment response and greater degree of repigmentation as well as reduction of cumulative UV exposure dose, le cons are additional time and costs, the fact that a proportion of patients will not profit, and long-term outcome not yet proven.

TARGETED PHOTOTHERAPY FOR VITILIGO

Giovanni Leone, Alessia Pacifico. S. Gallicano Institute IRCCS, Rome, Italy

Vitiligo is a common skin disease characterized by loss of normal melanin pigments in the skin and its pathogenesis is still unclear. Phototherapy, conventionally with psoralen and UVA (PUVA), or with the more recently reported narrow band UVB (NB UVB) with its wavelength of 311-313 nm, is the mainstay for generalized vitiligo. These treatments however, are associated with burning and skin ageing when administered for a long period. New ultraviolet sources capable of delivering large fluencies of narrowband ultraviolet B selectively to vitiliginous lesions in a shorter period of time have been introduced: this treatment modality has been defined as “targeted phototherapy”. Targeted phototherapy systems, which were first introduced for treating psoriasis, have recently proved their efficacy also for the treatment of localized vitiligo. Several investigations have documented the benefits of excimer phototherapy sources, which offer several advantages over conventional NB UVB units that irradiate both diseased and normal skin, whereas targeted light sources deliver high intensity light exclusively to depigmented areas. Rapid therapeutic responses have been reported, which may contribute to the reduction of the cumulative UV dose. Two systems emitting high energy have been developed: 308 nm excimer laser and a non-laser device (308 nm Monochromatic Excimer Light, MEL).

The 308 nm excimer laser emits high fluencies, which can be useful in thick plaques of psoriasis but not in vitiligo where only low fluencies are used. It is also possible to selectively turn the beam of light and thus to treat the specific area involved, sparing healthy skin. In vitiligo, this selectivity limits the unsightly tanning of perilesional skin, which is commonly observed with the other phototherapies. The liquid light guide (LLG) also makes it easier to reach areas that are usually difficult to treat, such as folds and mucosa. Disadvantages include the fact that the limited size of spots means that large surfaces (N20% of total surface body area) cannot be treated and that purchase and maintenance costs of these devices is rather expensive.

Good indications for the use of 308 nm MEL could be psoriasis and vitiligo with extended lesions, with an advantage over the laser that may be more time consuming. The cost of these devices is lower than that of lasers and maintenance is less frequently required. Nevertheless a comparative trial (308 nm excimer laser versus 308 nm excimer lamp) in a larger population is needed to clarify if the effectiveness of these two sources is the same.

Additional devices equipped with high pressure mercury arc lamps are now available for targeted phototherapy. The light is delivered to the skin by means of an optic fiber. Due to the emission spectrum of these lamps this is also referred to “targeted broad band UVB”. Interesting results have been described in vitiligo, with a high pressure mercury lamp capable of emitting either UVB or UVA. Furthermore, a targeted phototherapy device based on Selective Photo Clearing has been recently introduced. The Selective Photo Clearing is based on a new technology generating, by means of high power plasma light source, an emission at different wavelengths: 296-315nm, 360-370 nm, 405-420 nm. The system allows to select high intensity of UVB, UVA and a blend of targeted UVB and UVA1 delivered by means of a flexible LLG. UVA1 and UVB could act synergistically to induce repigmentation. The efficacy of this device has to be demonstrated with clinical studies. The major side effect of all targeted phototherapies is UV erythema. Higher therapeutic doses are commonly applied when treating lesional skin only, therefore erythema reactions may occur more often and with greater intensity than with NB UVB phototherapy. However, these reactions are confined to small areas of treated skin and do not impair the general well-being of the patient.

In conclusion conventional NB UVB remains the best treatment option for diffuse vitiligo; targeted phototherapy may represent a new therapeutic option for the management of non extensive vitiligo in order to achieve repigmentation in a shorter time and with better patients compliance as compared with other current modalities.

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PERSONAL VIEWS AND CONCLUDING REMARKS

Yvon Gauthier, Pigmentary disorders outpatient Clinic. Department of Dermatology. Bordeaux France.

The human skin is exposed daily to many environnemental factors. Among these factors the noxious influence of UV radiations on the skin has been largely investigated, but the importance of mechanical traumas has been often neglicted. Whatever the aetiology of the disease (autoimmunity, oxidative stress, neural hypothesis) vitiligo could be environnementaly « revealed » as a result of exposure to traumas. The incidence of the Koebner's Phenomenon (KP) assessed in different studies was very variable from 15% up to 70%, .because of a recall bias concerning the onset of depigmentation after scratches, burns, wounds. The best assessment method of incidence seems to be the experimentally induced KP phenomenon using scarification or a 2mm punch biopsy. Schematically several kinds of precipitating factors have to be identified in vitiligo: KP following an epidermodermal injury, KP occurring after superficial traumas without wounding such as repeated frictions and continuous pressure. At onset of vitiligo epidermodermal injuries appear to be required to induce « Koebnerization » but in extensive or rapidly spreading vitiligo, superficial traumas could be sufficient to induce depigmentation. KP is not exclusively a « vitiligo associated manifestation ». The study of KP could be useful 1) to assess disease activity 2) as a marker of an increased risk of vitiligo 3) to shed more light on the pathogenesis of vitiligo 4) to identify disease charasteristics that help predicting the outcome of therapies 5) to prevent the onset of new lesions and improve the repigmentation process
In conclusion, KP is as a fascinating process able to give the clinician many informations about the pathogenesis and the prognosis/course of the disease.

References :

Gauthier Y (1995) The importance of Koebner's phenomenon in the induction of vitiligo vulgaris lesions.Eur J Dermatol.5 :704-708

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Social programme (photographs)

After the VETF lunch session, the afternoon was devoted to a visit to Château de La Brède where the famous philosopher Montesquieu lived in the XVIIIth century, and from there, to a visit with wine tasting in the Sauternes wineyard (Château Guiraud, 1er grand cru classé).
The gala evening was held at Café Louis, within the National Opera House of Bordeaux, with the Opera Bastide artists.