Isfahan University of Medical Sciences, Dermatology, Isfahan, April 28, 2008

This offshoot of the 8th International Congress of the Iranian Society of Dermatology was held in picturesque Isfahan, a masterpiece of old Persia accented in majestic blue mosaic tiles. Many of its most important monuments date from 1051 as a principal city and capital of the Great Seljuk Empire stretching across the Middle East into the Indian subcontinent. Isfahan reached extraordinary prominence as the 16th century capital of united Persia under Shah Abbas the Great and his Safavid dynasty, dazzling the world with mosques, bridges and libraries of astonishing architectural splendor (Fig. 1). Today it is Iran's third largest city, renowned for its fine carpets, steel and experimental energy reactors. Thanks to the active support of the gracious Mohammad Reza Sabri, MD (Dean, Isfahan University of Medical Sciences) and encouragement of Professors Ali Asilian and Ali Z. Momeni, who assembled their faculty and dermatology residents, Professors Reza F. Ghohestani (USA), David A. Mehregan (USA) and Robert A. Schwartz (USA) were privileged to lecture at the Isfahan University of Medical Sciences (Figs. 2 and 3). Professor Manouchehr Sodeifi, Shiraz University of Medical Sciences, and journal scientific board member generously provided the impressive *Journal of the Isfahan Society of Dermatology* (Editor-in-Chief: Ali Asilian; Assistant Editor: Ali Z. Momeni), facilitating appreciation of Isfahan dermatology.

Figure 1. Magnificent Isfahan, the famous Khaju Bridge over the Zayandeh River, built in 1650 by Shah Abbas II, with intersecting arches and sluice gates that regulate water flow.

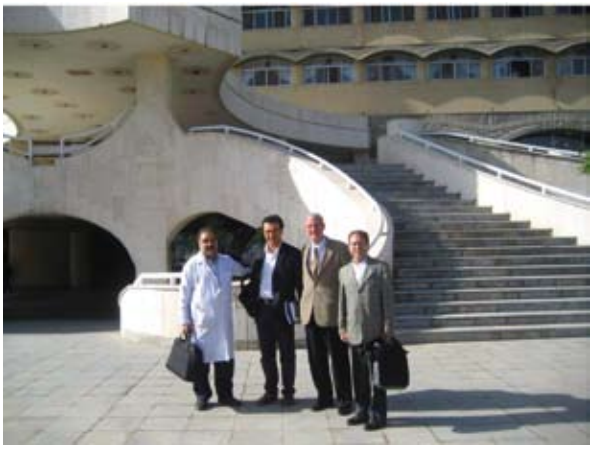

Figure 2. Alzahra University Hospital of the Isfahan University of Medical Sciences, Professors Ali Asilian, Reza F. Ghohestani, Robert A. Schwartz and Ali Z. Momeni (left to right).

The academic program consisted of three lectures. Prof. David A. Mehregan, son of the late internationally eminent Iranian professor of dermatology and dermatopathology Amir Mehregan, began with a talk on necrobiotic xanthogranuloma. He stressed its periorbital and flexural predilection, tendency to ulcerate, myeloproliferative associations, and distinctive dermatopathology. Professor Robert A. Schwartz covered tuberous sclerosis complex, emphasizing Fitzpatrick patches as its

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Figure 3. Dermatology, Isfahan University of Medical Sciences, with Prof. Reza F. Ghohestani in the center, Prof. Ali Asilian to his right, and seated man (right to left): Professors Ali Z. Momeni, David A. Mehregan and Robert A. Schwartz.

Figure 4. Isfahan in its opulent radiance, with Professors Jean-Claude Bystryn, David A. Mehregan and Robert A. Schwartz (left to right), in Imam Mosque on Imam (Naghsh-E Jahan) Square.

earliest manifestation and the potential use of sirolimus and its analogs. Professor Reza F. Ghohestani provided academic dermatology insights in Farsi. This scholarly program was supplemented by sightseeing of Isfahan, including the Imam Mosque of Shah Abbas the Great, one of the world's most glorious ones, on the south side of the inspirational Imam (Naghsh-E Jahan) Square – said to be home of the most stunning cluster of buildings in the entire Islamic world (Fig. 4).

The three invited speakers expressed their gratitude to Yahya Dowlati, Chairman of the 8th International Congress of the Iranian Society of Dermatology, for making this visit to Iran possible and wished colleagues in Isfahan every success in their upcoming First Congress of Anti-Aging and Aesthetic Medicine to be held in Isfahan on October 1-3, 2008 (www.spadanalaser.com).

Robert A. Schwartz, MD, MPH
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The First Two-Day Course on Dermatoscopy in Croatia

The First Two-Day Course on Dermatoscopy in Croatia was held in Zagreb, May 17-18, 2008, under conduction of Professor Harald Kittler from the Vienna University School of Medicine. The Course was held under the auspices of the Croatian Dermatovenereological Society, Croatian Medical Association, as part of the Euromelanoma Day Croatia project.

Over 140 dermatologists-venereologists and residents from Croatia participated in the Course with great interest. The Course was planned as one of the important events in the frame of the public preventive actions in line with the Croatian Euromelanoma Day and activities of the Dermatology-Venereology Committee of the Ministry of Health and Social Welfare of the Republic of Croatia and Croatian Dermatovenereological Society, Croatian Medical Association, to be held on June 6, 2008, sponsored by the La Roche Posay pharmaceutical company. All participants received a script with some practical data and morphological schemes as well as handouts of Professor Kittler's important lectures.

The first day started with a warm speech delivered by Professor Mihael Skerlev, president of the Croatian Dermatovenereological Society, followed by opening remarks and introductory lecture en-

titled "What to do with moles?", held by the Course leader, Assist. Professor Neira Puizina-Ivić from University Department of Dermatology and Venereology, Split University Hospital Center. The introductory lecture on the basic principles of dermatoscopy was held by Professor Kittler. In this interesting presentation, Professor Kittler pointed to the basic elements such as lines, pseudopods, circles, clods and dots. Their combinations make basic patterns – reticular, branched, parallel, radial and curved. Also, there is a structureless pattern. Symmetric combination of two patterns unusually means a benign course. The previous morphological mode of interpretation has in part been abandoned. Color analysis is also important. Black color corresponds to the presence of melanin and coagulated blood in corneal and epidermal layer. Dark brown color is a consequence of dense melanin in the epidermis. Yellow color indicates hyperkeratosis and corneal layer without melanin, whereas orange color is found in the presence of crusted lesion. Gray color provides evidence for the presence of melanin in papillary dermis, and we learned a mnemonic phrase that was often repeated: "gray is not OK". This facilitates recognition of malignant lesions. Blue color means that dense melanin is located in both parts of the dermis, whereas white is characteristic of sclerosis,

hyperkeratosis and absence of melanin. Combination of colors can assume a central, sporadic or eccentric pattern. The basic principles of pattern analysis include perceiving of these elements as guidelines to specific diagnosis. The first day was concluded with the interactive part of the Course.

At the beginning of the second day, Professor Kittler gave a short recapitulation of the previous day with highlights upon the most relevant issues. His excellent presentation of lesions at specific sites (palms, soles, nails and face) was very instructive for every participant. After a short and delicious break, a quiz with 50 dermatoscopic cases was distributed to the participants. After finishing, papers with answers were collected. A short but highly useful lecture on digital follow up was presented, depicting why and which nevi have to be followed-up. The papers with answers were randomly distributed to participants again and every participant corrected the form of another participant so cribbing was avoided. At the end, the winner with the highest number of correct answers was announced. The winner was Ranka Ivanišević, a resident from University Department of Dermatology and Venereology, Split University Hospital Center.

At the end, Professor Kittler made a proposal that three dermatologists proficient in German language could take part in the course on dermatoscopy to be held in Vienna in October 2008 free of charge. The participants showed great interest in the Course topic indeed. With his excellent, dynamic and very modern and innovative manner of presentation, Professor Kittler offered us an opportunity to share the Course activities with a high level and standards of presentation and methodology. La Roche Posay, Pharmaceutical Laboratory, under the leadership of hard-working Karmen Voda, BS, made this course full of positive energy. Most participants expressed their wish to repeat such a Course with some new and as attractive topic, which would help them in everyday practice, while greatly upgrading the quality of the Croatian dermatology-venereology.

Assist. Professor Neira Puizina-Ivić, MD, PhD

Keynote from Japan
5th Georg Rajka International Symposium on Atopic Dermatitis, Kyoto, May 11-13, 2008

In his Keynote Lecture, Thomas Bieber presented the hypothesis on atopic dermatitis (AD) as one or more severe diseases based on WHO classification of eczematous dermatoses developing before age 6 months and ending at age 3 years with early AD sensitization. The following issues were depicted: four AD subforms found in European population but not in Japanese patients: infancy, childhood, adolescence and adulthood; early onset and late onset; with genetic variant analysis revealing each of the overlapping gene loci of AD and asthma; with polymorphism in the filaggrin gene in ichthyosis vulgaris and AD (loss of function variants R 510x and 288 delta 4 in FFG gene in the epidermal biophysical barrier impairment; percutaneous sensitization in AD; role of staphylococcal aureus in IgE sensitization; AD as an autoimmune disease; role of gene-gene and gene-environment interaction in the natural history of AD; and environment allergens and autoallergy in AD (sensitization to self proteins) in nonatopic AD.

There are no uniform diagnostic criteria for AD. The Hanifin and Rajka (UK) diagnostic criteria have been most extensively validated; however, the Millennium Criteria from 1994, Japanese criteria, ISAAC criteria, and Lillenhamer criteria Schultz-Larsen, QUADAS Whiting *et al.*, 2003, are used in many studies. Up-to-date diagnostic criteria are needed to improve AD diagnosis to find visible phenotype of AD.

Controversies in AD are based on the following: **genetics** (HUGO; ATOD 1-6; 1q21, etc.); **pathogenesis** (barrier dysfunction and penetration of allergens and IgE sensitization, the immunocentric hypothesis on immune imbalance – IgE production – organ sensitization; **epidemiology** (different definitions in epidemiology; point prevalence *versus* period prevalence; not all age groups studied in all countries; explanation of increased AD prevalence, hygiene hypothesis: type 2 T-cell persistence after birth); **therapy** (tar preparation useful but carcinogenicity not studied, topical corticosteroids once or twice daily, pulse *versus* continuous corticosteroids, systemic corticosteroids frequent or never); **diagnosis** (WHO definition; atopy; atopiform dermatitis; uniformity of SCORAD, POEMS, EASI as confronting methods).

The ISSAC international study of asthma and allergies in childhood with 721,601 patients aged 6-14 from 156 centers and 56 countries based on UK diagnostic criteria showed a 5%-9.9% prevalence of ORs SPT positivity in flexural eczema to be associated with AD. Persisting AD, newly developed AD, regressing AD (70%) and non AD patients (5.5%) were differentiated. Disease activity in AD patients rather than the use of topical corticosteroids is responsible for the low baseline cortisol values in patients with severe AD and low bone mineral density in AD (about 30%), which is not related to the amount of topical corticosteroids used in the past. Plasma levels of platelet-derived microparticles (PDMP) and soluble P-selectin (sP-selectin), β-thromboglobulin (β-TG) and platelet factor 4 (PF_4) are determined as platelet activation markers in AD patients, however, plasma PDMP and sP-selectin may be markers of disease severity in AD. Filaggrin mutations are found in 50% of individuals with eczema as a risk factor for AD.

Raman spectroscopy is a rapid, noninvasive method providing detailed molecular information on tissues and predisposing factors for AD.

Psychological stress increases the production of endogenous glucocorticoids, and both systemic and topical agents can cause adverse effects or epidermal structure and function changes similar to those observed with psychological stress.

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Defects of the skin barrier are influenced by genetic defects of LEKTI in AD by a cluster of genes with general effects on dermal inflammation (1q21, 17q25, 20p, 3q21, 4q, 6p). Skin barrier function and expression of antimicrobial peptides in AD with pimecrolimus and betamethasone cream regulates the penetration of type I and type IV allergens into the skin.

Hot top key notes from the Symposium were: persisting AD since childhood accounts for up to 3% to 9%, with female predominance; filaggrin mutations in AD are a risk factor for asthma and AD with penetrance of 38%-40%; international consensus about the genetics, pathogenesis, epidemiology, diagnosis and therapy of AD is far from sufficient. Thymus-derived CD_4+CD_{25}+Fox p3+ natural T-regulatory cells play an important role in maintaining self-tolerance and preventing autoimmunity. The correlation of plasma levels of PDMP and sP-selectin with SCORAD index suggests that PDMP and sP-selectin may be markers of the disease severity in AD. The confocal Raman spectroscopy (noninvasive *in vivo* method) to indicate a filaggrin defect) is a rapid tool to screen infants for predisposing factors for AD and to detect reduced levels of NMF in stratum corneum.

Patients with atopic eczema have a genetic predisposition to enhanced protease activity. Topical corticosteroids induce increased protease expression in the skin, which is demonstrated by use of *in situ* zymography and RT-PCR.

Chemokines, small secreted molecules (more than 50) that regulate leukocyte trafficking *via* their corresponding seven-transmembrane spanning, G-protein coupled receptors, are involved in the pathophysiology of AD. AD patients are characterized by increased numbers of cutaneous lymphocyte-associated antigens (CLA) +CD_4 T-cells that directly affect the expression of skin homing genes in the total CD_4+ population. However, these CLA+CD_4+ T-cells differ qualitatively from those in healthy controls by decreased expression of apoptosis-related genes. Prostanoids are one of the lipid mediators that have a pathophysiological role in the body (PGE_2, PGD2, PG12, PGF_2 and thromboxane A_2); however, they also play a role in the skin antigen exposure and show a biphasic activity. Cyclosporine treatment *in vivo* was found to significantly decrease the percentage of CD_4 CD_{25} regulatory T cells and to reduce $FOXP_3$ and GADD45A expression in CD_4 + T cells from AD patients.

Interleukin-13 and interferon gamma producing skin resident CD_8 T-cells produce a vicious circle of barrier disruption of the skin in AD. Augmented interleukin-18 secretin may enhance the immune dysfunction observed in AD, leading to constant skin inflammation.

House dust mite (*Dermatophagoides pteronyssinus) (Dp*) can trigger allergic response through the increased expression of proinflammatory cytokines and cytokine measurement after DpE treatment may be used as a helpful screening system for the management of AD and other allergic diseases.

Allergen tests in AD are important to treat and care AD patients (atopy patch test, skin prick test, patch test, repeat open application test and use test). The wet wrap technique is a kind of occlusive treatment and is suitable for long-term treatment with a potent diluted corticosteroid cream in children as well as in adults, and is more effective than treatment with topical immunomodulators. Foods play an important role in irregular aggravation of skin lesions in children with AD. Infection of children with AD from their own emollients should be considered as a possible cause of recurrent infective exacerbations. More severely affected individuals may require systemic anti-inflammatory agents, particularly azathioprine or cyclosporine, mycophenolate mofetil and methotrexate, which may be associated with fewer side effects, and efalizumab has been shown promising among biologicals.

It was a very successful meeting organized by Japanese colleagues.

Professor Jasna Lipozenčić, MD, PhD

Reminiscence on the Post IID 2008 Satellite International Meeting on Autoimmune Bullous Diseases Otsu Prince Hotel, Japan, May 17-19, 2008

A hundred and twenty enthusiasts did their best to present the topic, having clarified it to some extent, however, yet remaining in part unexplained. The largest organ of the body, the magic skin, was highlighted at the International Meeting on Autoimmune Bullous Diseases, Otsu, Japan, May 17-19, 2008.

Could loss of Dsc3, a desmosomal cadherin function, be a cause of pemphigus vulgaris? Is Dsc 3 hl/pl a new born mutant? Desmoglein 1 (Dsg1) silencing impairs differentiation and morphogenesis of suprabasal keratinocytes. Desmoglein 1 adhesive ectadomain is dispensable for differentiation of keratinocytes. Desmoglein 1 and 2 act as the Yin and Yang of epidermal differentiation. Dsg1 regulates GF and acting remodeling pathway *via* cortactin during keratinocyte differentiation.

In fogo selvagem (FS) there is a prevalence of IgG AND IgM anti Dsg1 antibodies. In FS cases IgM prevail over IgG in neonates; however, in Japan IgG prevail over IgM. IgG_4 is a predictor of FS. In pemphigus, there are structural determinants of autoantibody pathogenicity and restricted antibody variable region genes.

Immunoglobulin E has a role, along with BP 180 antibody, in bullous pemphigoid. The dermis contains free BP 180 antigen as a proteolytic fragment. IgE antibody to BP180 fragments binds to mast cells.

In EBA there is an autoantibody response. IgG to type VII collagen induces subepidermal blisters, as indicated by passive transfer of IgG from EBA patients. Patients with anti p 200 pemphigoid have positive laminin γ_1 monoclonal antibody in the skin and vessels as an exclusive p200 antigen. In pemphigus, acantholysis is caused by Dsg and non-Dsg factors; synergic Dsg and nonDsg action is present and nonDsg-like acetylcholine should be used as a model for further research. The role of tight junction (TJ) in epithelial barrier function was elucidated through claudin-based tight junction. An ubiquitin E_3 ligase LwX_1 may be involved in the turnover of TJ by internalization and degradation of claudins in the skin. Single molecule tracking in the living cell membrane: signaling in a variety of membrane domains. The role of p 38 MAPK signaling in pemphigus is necessary. Is p 38 MAPK kinase primary or secondary event of acantholysis? Increased phosphorylation of p 38 MAPK is found in pemphigus vulgaris IgG. Inhibitors of p 38 MAPK block pemphigus vulgaris IgG internalization. The gain or loss of cell-cell adhesion initiates a signal transduction cascade up to actin filaments.

Pemphigus foliaceus IgG do not directly inhibit Dsg1 transinteraction. Pemphigus vulgaris IgG and AK 23 directly inhibit Dsg1, and PV IgG reduce binding of Dsg3 and DSg 1 to the surface of keratinocytes. Signaling is primary directed to acantholysis. Catenin p-120 is a possible new intracellular signaling mediator in pemphigus acantholysis. Desmoglein 3 reactive T-cells: a key player in the autoantibody production has been proved in a mouse model with immunotolerance in mouse with rDsg3 in footpad. HLA class II-transgenic mouse is an *in vivo* model for cellular and humoral immune response to humoral desmoglein 3 in pemphigus vulgaris – HLA-DRO 402-DQ 8. Rituximab (375 mg/m^2 1, 8, 15, 22 d) and IVIG (2 g/kg/6 months) are powerful new treatment options for acute recalcitrant pemphigus vulgaris patients. It is suggested that a novel rituximab treatment protocol for PV would be better with only twice application of 500 mg or 1 g/kg for 4 days. IVIG as monotherapy with variable dosage of 200 mg or 400 mg showed no difference. It is suggested day 80 of treatment is the “time to escape from

the protocol". Pemphigus scoring system (PSS) was found to be most relevant: ABSIS scoring sheet; PDAI and PGA (physician Global Score). Data on pemphigus vulgaris should be entered in a database, preferentially also in Croatian. Again, we wish to congratulate the Japanese colleagues on the excellent organization of such a successful conference on autoimmune diseases.

Assist. Professor Branka Marinović, MD, PhD
Professor Jasna Lipozenčić, Md, PhD

Under the auspices of

Academy of Medical Sciences of Croatia
Ministry of Health and Social Welfare of Croatia
Zagreb Clinical Hospital Center
University of Zagreb, School of Medicine, Croatia

University Department of Dermatology and Venereology

organizes

Ceremonious Assembly in occasion of 80 years continuance of University Department of Dermatology and Venereology, Zagreb University Hospital Center and School of Medicine

Zagreb, Croatia, December 9, 2008 at 10,00 a.m.
Lecture Room of University Department of Dermatology and Venereology,
Šalata 4, 10000 Zagreb